The Official Journal of The Life Raft GROUP

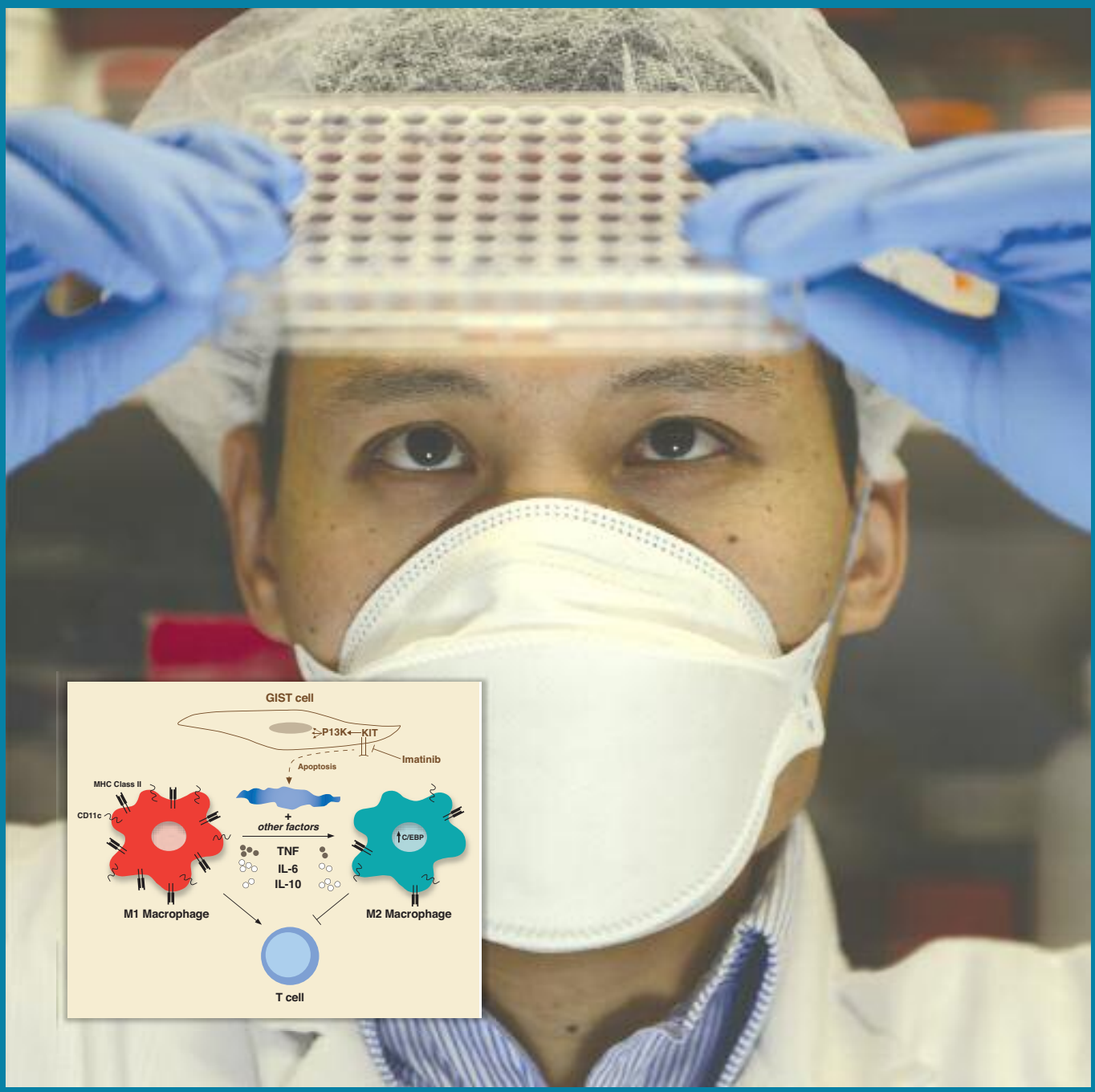
The GIST Cancer Journal

www.thegistcancerjournal.org Volume 1, Number 4 Winter 2014

Immunotherapy Drives a Paradigm Shift Toward New Model of Treatment

New Perspectives on GIST in the Era of Histology Codes

Strategies to Manage Side Effects of TKI Treatment



An Educational Service for Medical Oncologists, Gastroenterologists and other GIST Care Providers

Editorial Mission
The GIST Cancer Journal is intended to serve as a comprehensive and authoritative resource of scientifically valid information for physicians and allied health care professionals regarding advances in the diagnosis and treatment of gastrointestinal stromal tumors. Editorial content focuses on the impact of translational research in oncology and gastroenterology relating specifically to GIST. As the official medical journal of the Life Raft Group, it also provides a forum for GIST patient advocacy. *The GIST Cancer Journal* is circulated to all medical oncologists and other selected medical professionals, and is available to members of the GIST community upon request

The Life Raft Group
The mission of the Life Raft Group is to ensure the survival of GIST patients through a comprehensive approach connecting individual patients' needs, the worldwide community of GIST advocates and the global health and research environment. To do this, the group focuses on three key areas: research, patient support and education, and advocacy. (For additional information, please see Page 15.)

The Life Raft Group
155 Route 46 West, Suite 202
Wayne, NJ 07470 USA
Phone 973-837-9092 ; Fax 973-837-9095
E-mail liferaft@liferaftgroup.org

Publishing Staff
Stu Chapman, Executive Editor and Publisher
Jenny Chapman, Assoc. Director, Editorial Services
Frank Iorio, Director of Advertising Sales and Business Development
Gloria Catalano, Production Director
Michael McClain, Design Director

Editorial Office
GUP Associates
2557 Tulip Street
Sarasota, FL 34239
Tel: (516) 356-5006

About the cover
Immune-mediated therapies in development, as represented by this laboratory researcher examining wells containing cell cultures for possible contamination, could have a sharp impact on the spectrum of treatment. Smaller image highlights pathways of current treatment with tyrosine kinase inhibitor, imatinib. (Photo courtesy of Jonathan C. Trent, MD, and Luyuan Li, PhD.)

Table of Contents

Editor's Memo

Looking Beyond the 'Media Hype' on Immunotherapy and Assessing Implications for GIST

Virtually every report coming out of an oncology meeting or posted on an oncology website these days seems to highlight the importance of immunotherapy. Judging from the media hype, a new drug is on the verge of getting "fast track" status from the FDA or moving further along in the pipeline of research and development. Although it is the dominant trend discussed at scientific meetings, these novel therapies, such as the recent announcements surrounding nivolumab in different tumors, still need further verification in clinical trials before application to a broader spectrum of tumors. Much work is still needed at the bench before we can even think of integrating such approaches into the treatment paradigm for a disease like gastrointestinal stromal tumor (GIST).

Nevertheless, concepts like "designer T cells" and "chimeric antigen receptors" may soon be working their way into our lexicon, competing with earlier principles of therapy such as tyrosine kinase inhibition and anti-angiogenesis. Immunotherapy is in vogue but it has a long history. Its potential application in GIST, however, is just beginning to be realized and it is important to keep abreast of new information such as the findings highlighted by Ronald DeMatteo, MD, in this issue of our journal. Applications of immunotherapy, perhaps even combined with targeted approaches, could soon be within our grasp. At least they are on the horizon. It's all part of the so-called new era of "personalized therapy," a term that has been overworked by the media but has not lost its luster when it is used in the consumer press, exciting hope among practitioners and patients alike.

But most practicing community oncologists are still aware that many trials are still in the xenograft stage as we discover more about the tumor microenvironment in mouse models and how the interplay of intratumoral

(continued on next page)

The GIST Cancer Journal Author Guidelines

Scope of Manuscripts
The GIST Cancer Journal considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Original contributions based on original, basic, clinical, translational, epidemiological, or prevention studies relating to gastrointestinal stromal cancer that are well documented, novel, and significant.
- Letters to the Editor on timely and relevant subjects pertaining to the diagnosis and treatment of gastrointestinal stromal tumor.
- Clinical case studies.

Manuscript Submission
Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Jonathan C. Trent, MD, PhD at jtrent@med.miami.edu. Please provide in a word processing program. Images should be submitted electronically as well.

All material reproduced from previously published, copyrighted material should contain a full credit line acknowledging the original source. The author is responsible for obtaining this permission.

Contact information
List all authors, including mailing address, titles and affiliations, phone, fax, and email. Please note corresponding author.

Peer Review and Editing
Manuscripts will be peer reviewed. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with American Medical Association (AMA) style. Authors whose manuscripts are not initially accepted may have the opportunity to revise the manuscript based on recommendations from peer reviewers and at the discretion of the Editor-in-Chief.

Conflict of Interest
The GIST Cancer Journal policy requires that authors reveal to the Editor-in-Chief any relationships that they believe could be construed as resulting in an actual, potential, or apparent conflict of interest with regard to the manuscript submitted for review. Authors must disclose this information in the covering letter accompanying their submission.

Manuscript Preparation
Length: Full-length manuscripts should not exceed 4000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally 4-5 figures and 2-3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a legend for all abbreviations. Manuscripts should not contain an abstract but an introduction is recommended.

Spacing: One space after periods. Manuscripts should be double spaced.

References
All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style.

Example:
Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest*. 2001;119:818-823.

Copyright

Editor's Memo *(continued from page 102)*

immune cells—once validated in randomized trials—could actually translate into effective treatment. If translational research achieves greater efficacy we will have yet another piece of the puzzle in optimizing our treatment options.

There are other pieces of the GIST puzzle also emerging, as disclosed in the first of a two-part series in or journal on risk factors and epidemiology, as outlined by Jason Sicklick, MD. As the histology codes for GIST have changed, a clearer picture of the epidemiology of the disease has been revealed. Again, one more piece of the puzzle. Earlier misconceptions about GIST no longer confuse those who need to delineate its features and distinguish it from other tumors. By elucidating these features and better identifying groups at risk, patients can be followed earlier and intervention planned appropriately. We are pleased to provide readers with an update in these areas as part of our continuing commitment to expanding an awareness of evidence-based trends in GIST diagnosis and treatment.

Jonathan C. Trent, MD, PhD
Editor-in-Chief

Immunotherapy Drives a Paradigm Shift Toward a New Model of Treatment

Ronald DeMatteo, MD, FACS
Vice Chair, Department of Surgery
Head, Division of General
Surgical Oncology
Leslie H. Blumgart Chair in Surgery
Memorial Sloan-Kettering Cancer Center
New York, New York

Stu Chapman
Executive Editor
The GIST Cancer Journal

A few years ago concepts like "designer T cells" and "chimeric antigen receptors" sounded somewhat like a foreign language. This is no longer true as immunology-based reports in GIST have reshaped our understanding of the biology underlying the disease. At the bench, immune-mediated therapies are now based on more than mere hypotheses. However, these novel therapies are not yet ready for widespread clinical use and need to be verified in additional clinical trials. But if recent and ongoing studies can help chart future directions, a new era in GIST treatment may be within our grasp sooner than most clinicians expected.

An explosion of new treatment approaches using innovative immunomodulating strategies is providing insights into how the treatment of many cancers, and GIST specifically, could undergo vast and even revolutionary changes. The timing could not be better for the management of GIST. Although it has long been recognized that the immune system contributes to tumor development and control of tumor growth,[1] the rationale for its use in GIST is driven by a dramatically improved understanding of the biology of the disease and how cell-mediated mechanisms could be manipulated to resolve the longstanding conundrum of resistance to imatinib therapy.

Since 2001, as suggested by some authors, GIST may be considered a role model for the use of molecularly defined therapies in solid malignancies.[2] In contrast to the pre-imatinib era,[3] discoveries of a biomarker identified through KIT immunohistochemistry and introduction of imatinib, a highly specific tyrosine kinase inhibitor, meant that clinicians began looking at GIST as a potential paradigm for the development of personalized therapies against cancer.[4] Now it appears we are on the threshold of a new era in personalized therapy with the potential introduction of immunotherapies. For example, anti-Kit antibodies have been developed, engineered so that such treatment could be reinserted into a patient with GIST, could reduce cell-surface KIT expression and may inhibit GIST growth. GIST could be one of the next diseases in which such novel immune strategies prove effective, much as they are already suggesting benefit in melanoma, lung cancer and kidney cancer. Most of the recent reports contributing to an evolution in thinking can best be divided into two areas: (1) there is an improved understanding of the biology of the disease; and (2) there is growing optimism that immunotherapies could be used in combination with imatinib and could potentiate antitumor T cell responses via their synergistic effect.

It may be, for example, that imatinib could be used in combination with the new checkpoint inhibitors or CTLA-4 inhibitors, both of which appear to serve as models of how immune-based therapies could improve outcomes. Inhibition of PD1 and PD-L1 have produced significant improvement in outcomes in melanoma, lung cancer, and kidney cancer and new molecules are expected to broaden the spectrum of therapy in solid tumors. Although these diseases have been the primary focus of investigative efforts on checkpoint therapies, there is a window of opportunity envisioned for GIST clinical trials as well. For example, there is a CTLA4 trial already in progress.

Among the most frequently asked questions is how such new trials in GIST will be shaped by the preclinical results that point to an improved understanding of the biology of the disease, particularly from an immunotherapeutic perspective. These published reports, albeit in mouse models and human GIST specimens models, are shaping the dynamic of the new efforts to develop effective immune-based approaches. Reports within the last few years have revealed much more about the tumor microenvironment, the interplay of factors involving intratumoral immune cells in GIST, and what could improve the suboptimal potency of currently available inhibitors.

Biology: NK Cells, Macrophages, T Cells and Much More

Tumor-associated macrophages (TAMs) play a central role in cancer biology because they constitute a substantial portion of the tumor mass and interact with numerous effector cells.[5] The role of TAMs, their function, and their impact on prognosis in GIST is under intense investigation because of important implications for immunotherapeutic strategies not

(continued on page 106)

COMING SOON

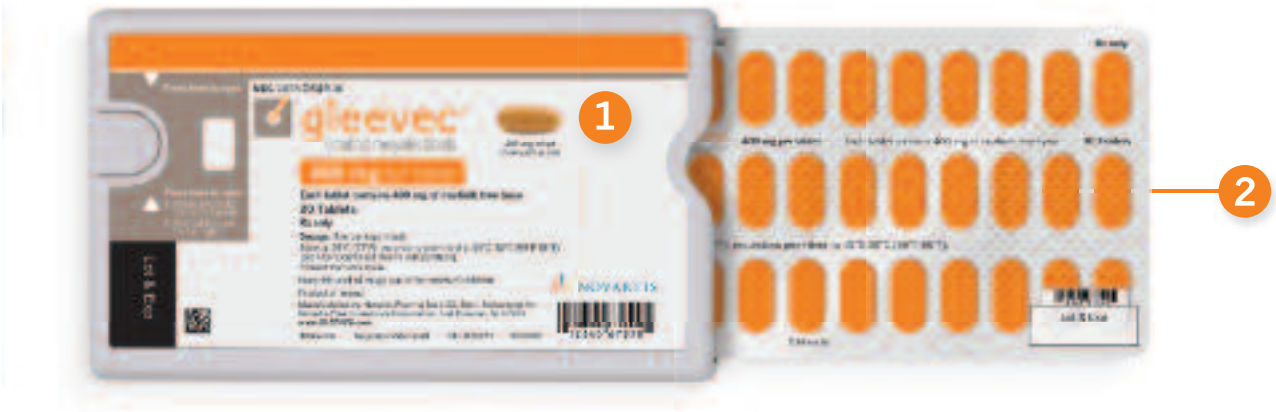
We stand by the name:

The **name you trust will be on the tablet** you prescribe

Novartis Oncology is proud to inform you of the **new GLEEVEC® (imatinib mesylate) packaging and a new look for the 400-mg tablet** that will soon be available for your patients.*

The new tablet and packaging will feature:

1. **400-mg tablet debossed** with the trusted **GLEEVEC name**
2. **New blister pack** that helps your patients keep track of their dosing regimen



The formulation, dosage strength, and dosing instructions for GLEEVEC will remain the same. Visit **www.GLEEVEC.com** for more information.

*The 100-mg GLEEVEC tablet will not change, and it will continue to be dispensed in a pill bottle.

NOVARTIS ONCOLOGY

gleevec® (imatinib mesylate) tablets 100mg, 400mg

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 10/14 GLI-1098265

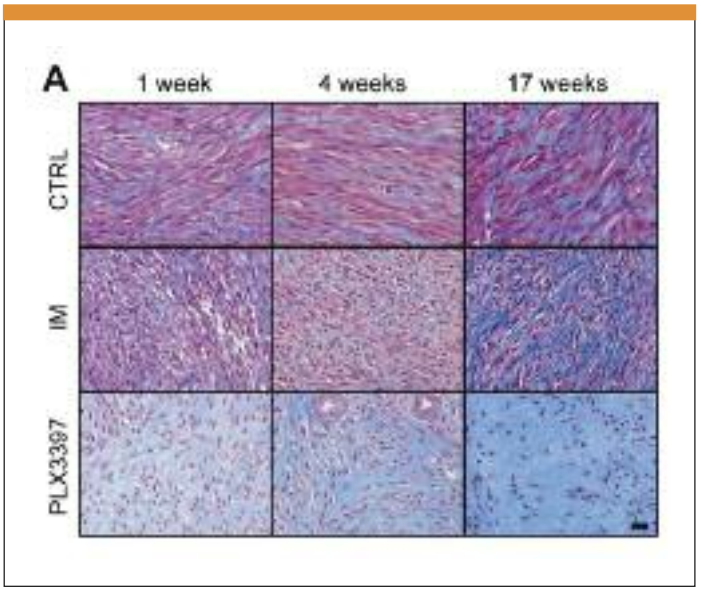
only in GIST but other cancers. TAMs comprise a substantial portion of intratumoral leukocytes. There are basically two categories of macrophages: M1 or tumor-inhibitory, and M2, tumor promoting.

TAMs have an intricate biology, and recent reports elucidate why TAMs are a potential immunotherapeutic target and how their response to imatinib could provide clues to their gene expression profile, raising implications for treating GIST. Evidence from Cavnar et al. also help to clarify whether such strategies like TAM depletion may be effective. TAMs are present in high numbers in both mouse and human GISTs.[6] A key issue is whether TAM depletion could provide an additional treatment option to imatinib. Although the KIT oncogene is initially highly sensitive to imatinib, leading to partial response or stable disease in approximately 80% of patients, with metastatic disease, the median time to progression or imatinib resistance is about 2 years because of additional KIT mutations.

Cavnar et al. studied a mouse model of GIST and 57 freshly procured human GISTs. They found that TAMs displayed an M1-like phenotype and function at baseline. However, in both mice and humans, imatinib polarized TAMs to become M2-like; this involved a process characterized by TAM interaction with apoptotic tumor cells leading to induction of CCAAT/enhancer binding protein transcription factors. In human GISTs that became resistant to imatinib, TAMs reverted to an M1-like phenotype and had a gene expression profile similar to those from untreated GISTs. This evidence of TAM polarization opens a new avenue to investigation. The discoveries by Cavnar et al. reveal more about the plasticity long considered a striking feature of macrophage biology. This is evidence that GIST-associated macrophages undergo a remarkable phenotype shift in response to imatinib therapy.

One of the unresolved issues is whether strategies involving TAM depletion may be beneficial. Several concepts are clear: functionally, TAMs from untreated and resistant human tumors uniformly stimulate T cell proliferation, while TAMs from some sensitive tumors suppress T cell proliferation. This is consistent with their shift toward an M2-like gene expression profile, according to Cavnar. Thus, TAMs have been found to be M1-like in untreated tumors, shifting to M2-like in tumors responding to imatinib, but ultimately, they revert to M1-like in GIST tumors acquiring resistance. This leaves unresolved the debate over whether TAM depletion is beneficial and how the issue of TAM polarity should be put into proper perspective.

TAM polarity in human cancers is more complex than initially thought. The mechanisms are complex, and TAMs exhibit dynamic phenotypic and functional stratification—possibly related to tumor histology as well as location and prior therapy. Further studies will need to explore these controversies. For now, Cavnar et al say TAM depletion may yield benefit in several human cancers, but in others, like GIST, targeted TAM depletion may not help. The findings so far are provocative and serve as a basis for further studies to determine the clinical relevance of TAM polarization in GIST.



The images here depict the stromal response to PLX3397, a novel agent which inhibits KIT and has been hypothesized to be more effective than imatinib. After 17 weeks, collagen accumulation was dramatic. But imatinib-treated mice tumors accumulated collagen more slowly and to a lesser extent and untreated tumors maintained only a constant, low level of collagen. The findings illustrated here suggest a final common pathway of tumor cell-mediated collagen deposition and tissue remodeling caused by KIT inhibition in GIST.

NK Cell–dependent Antitumor Effects Promoted by Imatinib

Additional insights on the biology of GIST and immune-based effects of imatinib have emerged from a group of French investigators led by Laurence Zitvogel. Their reports on the role of natural killer (NK) cells amplify our understanding of the importance of imatinib's indirect immunostimulatory effects on T cells and NK cells.[7]

Although evidence for a natural killer (NK) cell-based control of human malignancies is still largely missing, this area of research is undergoing tremendous change. In their report, Rusakiewicz et al demonstrated that imatinib markedly prolongs the survival of patients with GIST by direct effects on tumor cells as well as by indirect immunostimulatory effects on T and NK cells. They investigated the prognostic value of tumor-infiltrating lymphocytes (TILs) expressing CD3, Foxp3, or NKp46 (NCR1) in a cohort of patients with localized GIST. Their results suggested that CD3(+) TILs were highly activated in GIST and were especially enriched in areas of the tumor that conserve class I MHC expression despite imatinib treatment. High densities of CD3(+) TILs predicted progression-free survival (PFS) in multivariate analyses. Moreover, GIST was infiltrated by a homogeneous subset of cytokine-secreting CD56(bright) (NCAM1) NK cells that accumulated in tumor foci after imatinib treatment. The density of the NK infiltrate independently predicted PFS and added prognostic information to the Miettinen score, as well as to the KIT mutational status. NK and T lymphocytes preferentially distributed to distinct areas of tumor sections and probably contributed independently to GIST immunosurveil-

lance. These findings encourage the prospective validation of immune biomarkers for optimal risk stratification of patients with GIST.

The French group has produced other findings that expand on these associations. For example, in another paper Delahaye et al[8] examined to what extent the natural killer (NK) cell receptor NKp30 is involved in the recognition of tumor and dendritic cells (DCs). The influence of three NKp30 splice variants on the prognosis of GIST was evaluated since GIST has been found to express NKp30 ligands. Healthy individuals and those with GIST show distinct patterns of transcription of functionally different NKp30 isoforms. In a retrospective analysis of 80 individuals with GIST, predominant expression of the immunosuppressive NKp30c isoform (over the immunostimulatory NKp30a and NKp30b isoforms) was associated with reduced survival of subjects, decreased NKp30-dependent tumor necrosis factor- (TNF-) and CD107a release, and defective interferon- (IFN-) and interleukin-12 (IL-12) secretion in the NK-DC cross-talk that could be restored by blocking of IL-10. Thus, it may be that genetically determined NKp30 status predicts the clinical outcomes of individuals with GIST independently from *KIT* mutation.

In a related paper, Menard et al[9] reviewed data on the off-target effects of imatinib such as triggering natural killer (NK) cell activity. The intriguing aspect of this report is that, unlike other hypothesis-generating papers, this one could have practical merit since it determined whether NK cell functions could predict long term survival with imatinib. NK cell functions were followed up in 77 GIST patients enrolled in two phase 3 trials. "Immunologic responders" were defined as patients whose NK cell IFN- values after 2 months of imatinib were higher than or equal to the baseline value at entry into the trial. The prognostic effect of IFN- on progression-free survival was assessed by a Wald test in a Cox regression analysis using the landmark method and stratified by trial and on the *KIT* mutational status.

As early as 2004,[10] case reports of clinical efficacy of imatinib in GISTs lacking the typical receptor mutations prompted a search for an alternate mode of action. Imatinib can act on host DCs to promote NK cell activation. DC-mediated NK cell activation is reported to be triggered in vitro and in vivo by treatment of DCs with imatinib as well as by a loss-of-function mutation of KIT, according to Borg et al. Therefore, tumors that are refractory to the antiproliferative effects of imatinib in vitro responded to the drug in vivo in an NK cell-dependent manner. Longitudinal studies of imatinib-treated GIST patients revealed a therapy-induced increase in IFN-gamma production by NK cells, correlating with an enhanced antitumor response. These data point to a novel mode of antitumor action for imatinib.

In the search for additional prognostic factors, Borg et al addressed whether imatinib could exhibit functional side effects on KIT expressing the targets of the host. Indeed, tumor cell progression not only depends on cell autonomous tumor suppressive pathways but also on extrinsic immunologic barriers.[11] Borg et al highlighted an alternate mode of action of imatinib that is not tumor cell autonomous and involves—at least—host bone marrow–derived dendritic cells. In identifying that mode of action, the authors purport to unravel the natural killer (NK) cell–dependent antitumor effects promoted by imatinib-treated DCs in mouse tumor models resistant to the imatinib antiproliferative effects *in vitro.*[12]

A Marker for Prognosis: Blood Neutrophil-to-Lymphocyte Ratio

The search for peripheral biomarkers that could translate into a useful clinical tool has uncovered important information with possible practical merit. Previous evidence showing that imatinib increases the intratumoral ratio of CD8T cells to T regulatory cells[13] is part of additional emerging data that could yield insights on the interaction between cancer cells and neutrophils, a proposition often poorly understood. Although knowledge about regulatory mechanisms in cellular immunity has vastly improved, it is still uncertain whether cancer therapy utilizing a neutrophil-mediated approach is valid. In addressing this issue, a paper by Balachandran offered several key immune findings. Imatinib works in part by altering IDO, an immune suppressive enzyme made by tumor cells. T cells within GISTs depend on treatment response. The ratio of CD8T cells to T regulatory cells is increased by imatinib. Lastly, anti-CTLA4 plus imatinib is synergistic, which prompted a current NCI trial in GIST.

A study at our institution[14] considered the value of the neutrophil-to-lymphocyte (NTL) ratio in blood because it is an easily accessible parameter of systemic inflammatory response. The goal was to determine if it could be used as a prognostic factor in GIST. Perez et al identified 339 previously untreated patients with a primary, localized GIST operated at Memorial Sloan-Kettering Cancer Center between 1995 and 2010. Patients who received adjuvant imatinib treatment (n=64) were excluded from the survival analysis. Four patients had an incomplete set of blood values and were excluded as well. Recurrence was defined as evidence of disease relapse on CT or MRI and/or positron emission tomography (PET).

Preoperative peripheral blood samples were collected within 10 days before surgery. No patient had clinical signs of infection at the time of blood sampling. Blood NLR was calculated as neutrophil count (number of neutrophils/ L) divided by lymphocyte count (number of lymphocytes/ L). A significant correlation was observed between blood NLR and mitotic rate (Pearson correlation coefficient (r)=0.15, P=0.03). An even stronger correlation was found between NLR and tumor size (r=0.36, P=0.0001). Recurrence-free survival in patients with a GIST >5 cm with low NLR was significantly longer compared to patients with high NLR (P=0.002). Although the results need to be confirmed, it appears that a systemic inflammatory response in untreated patients correlates with a high risk GIST. This suggests that NLR is a surrogate for poor prognosis in GIST and may represent a valuable parameter for predicting tumor biology from peripheral blood. The mechanism of neutrophilia in high risk GIST, however, remains unclear.

Beyond Biology: Future Directions in Therapy

It is speculation at this point and well justified considering the emerging evidence, but therapy for GIST will be radically different than it is today with new reports pointing the way toward innovations in treatment that include such approaches as designer T cells (dTc), anti-KIT monoclonal antibody, and combinations of imatinib and immunotherapy.

Anti-KIT Monoclonal Antibody (mAbs): Targeting Downstream Signaling

The focus on improving small-molecule drug candidates for GIST and other cancer has turned toward the potential benefit of mAbs. mAbs can exert multiple, and often simultaneous, effects on cancer cells via their interaction with their targets.[15] These mAb-induced interactions can ultimately combine to produce antitumor effects in vitro and in vivo through various modes of action, including inhibition of the target's ability to activate downstream signaling targets, internalization and degradation of a cell-surface target, phagocytosis, and/or antibody-dependent cell-mediated cytotoxicity (ADCC), a process through which target cells are lysed by cytotoxic granules released by natural killer (NK) cells, granulocytes, and other leukocytes.[16]

In a pivotal study, one that eventually could be considered a landmark in its findings for mAbs, Edris et al[15] showed that treatment of GIST cell lines with the anti-KIT mAb SR1 resulted in a significant decrease in cell growth and in cell-surface KIT expression; they suggest that the SR1-mediated growth inhibition in GIST cells may be occurring due to internalization and degradation of KIT. Another key finding was that SR1 treatment increased phagocytosis of GIST cells by macrophages. Further study is needed, however, to definitively identify additional consequences of SR1 treatment on GIST cells.

The impact of SR1 treatment on GIST cell interactions with additional immune effector cells, such as T-cells, B-cells, and NK cells, which were not present in the mice used in this group's xenotransplantation studies, needs to be investigated. In the future, SR1, or other KIT-specific mAbs, could be modified to enhance affinity to KIT and/or to potentiate one or more mAb-mediated antitumor cell functions, such as receptor internalization, receptor homodimerization inhibition, macrophage phagocytosis, or ADCC, according to Edris et al. The study could have further ramifications: it focused on treatment of GIST cells, but SR1 or other anti-KIT mAb treatment that may prove useful in other KIT-positive tumors, such as pancreatic adenocarcinoma, testicular seminoma, melanoma, neuroblastoma, and breast cancer.[17-21]

Designer T Cells and the Chimeric Immune Receptor

Among the most exciting results produced within the last two years concerns advances in cell-based immunotherapy using tumor infiltrating lymphocytes (TIL). The potential impact of TIL therapy has been limited by the inability to isolate TIL from the majority of patients with solid tumors.[22] The genetically modified or designer T cell (dTc) strategy facilitates production of tumor-specific lymphocytes for any patient with a suitable target tumor antigen. Katz et al explored the potential of previous work in which lymphocytes were isolated from peripheral blood and activated prior to retroviral transduction with a chimeric immune receptor (CIR) gene.[23] Expression of CIR on the surface of modified T cells allows for highly specific recognition of tumor cells expressing the cognate antigenic moiety. Previous reports demonstrated that retrovirus mediated introduction of tumor has resulted in dTc capable of activation, cytokine secretion, and target cell lysis.2[4-26] Clinical success has recently been reported using dTc for the treatment of soft tissue sarcoma, melanoma, and leukemia.[27,28] The report by Katz et al delineates[29] how the use of dTc could translate into effective targeting of tumor in GIST:

- CIR typically exploit immunoglobulin or T cell receptor based specificity to target tumor antigens. Using an alternative strategy, the team engineered a CIR that contains the natural ligand for KIT, which allows for recognition of KIT+ tumor cells.
- KIT-ligand (KL) or stem cell factor (SCF) was fused to the CD3 chain component of the T cell receptor (1st generation, 1st gen) or CD3 + the CD28 co-stimulatory molecule (2nd generation, 2nd gen). The 2nd gen dTc express the construct that targets KIT+ tumors while, at the same time, integrating CD28 co-stimulatory signals. These are designer T cells but they are not chimeric antigen receptor T cells. The cells express the ligand for KIT but do not actually target a specific antigen on the tumor cells.
- 1st and 2nd gen dTc were produced and tested *in vitro* and *in vivo* to demonstrate their efficacy in destroying KIT+ tumor cells. Katz et al demonstrated encouraging initial results for anti-KIT dTc which could provide the rationale for further pre-clinical testing of this novel immunotherapeutic anti-tumor agent.

Katz et al speculate[29] that tumor cell lysis, antigen release, and the associated inflammatory response may stimulate endogenous immunity which may contribute to tumor regression. The implications of a normal endogenous immune system for the *in vivo* activity of anti-KIT dTc require clarification through additional studies as well as consideration of the use of this approach in combination with imatinib which has also been shown to produce immune modulating action.

PLX3397: A More Potent KIT Inhibitor

If one were to devise an ideal strategy for GIST it would probably involve enhanced KIT inhibition perhaps combined with an immune-mediated focus as well, offering a two-pronged approach to overcoming imatinib resistance. Although the study[30] was done in mice, experiments with PLX3397 (Plexxicon) a KIT and colony-stimulating-factor-1 receptor (CSF1R) inhibitor, suggest that this molecule could eventually be among new agents destined for clinical application. Results were encouraging in this preclinical study: PLX3397 (**Figure**) was more effective than imatinib in reducing tumor weight and cellularity in both Kit(V558del)(/+) murine GIST and human GIST xenografts. The superiority of PLX3397 did not depend on depletion of tumor-associated

macrophages, because adding CSF1R inhibition did not improve the effects of imatinib. Instead, PLX3397 was a more potent KIT inhibitor than imatinib in vitro. PLX3397 therapy also induced substantial intratumoral fibrosis, which impaired the subsequent delivery of small molecules.

Combining Interferon With Imatinib

A report by Chen et al[31] is a good example of why new literature is likely to reflect a growing number of studies investigating the potential use of imatinib in combination with immunotherapy to induce antitumor immunity. Advances in tumor biology undoubtedly will lead to discovery of more effective targeted therapeutic agents in the future, but drug-resistance and early relapse will undoubtedly maintain recurrent themes using monotherapy. Recognizing the limitations of monotherapy, Chen et al combined peg interferon -2b (an immune modulator and a danger signal) with imatinib in a GIST model and demonstrated significant induction of innate and Th1 response along with a highly promising clinical outcome.[6]

This combination treatment was well tolerated, safe, and induced significant IFN -producing-$CD8^+$, -$CD4^+$, -NK cell, and robust IFN -producing-tumor-infiltrating-lymphocytes, signifying induction of innate and Th1 adaptive cell-mediated immunity (Th1 response).[32] Complete remission (CR) + partial response (PR) = 100%; overall survival = 100%; one patient died of unrelated illness while in radiographic near-CR; after a median follow-up of 3.9 years, five of the seven evaluable patients are in continuing PR/CR with duration more than doubling the median-genotype-specific-PFS of the Phase III IM-monotherapy trial (CALGB150105/SWOG S0033).

Conclusion

GIST has often been referred to as a model for the use of targeted, molecularly defined therapies for solid malignancies. The new development in GIST treatment revolves around the use of immune-mediated approaches and provocative concepts in management emerging because of an improved understanding of disease biology. With this improved understanding of a range of factors, such as tumor-associated macrophages and how these cellular mechanisms are interrelated, their translational impact has manifested in innovative immune-mediated strategies that could reshape traditional management and set the stage of more effective management of GIST.

References

1.Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol.* 2004;22:329-360.

2. Kitamura Y, Hirota S, Nishida T. Gastrointestinal stromal tumors (GIST): A model for molecule-based diagnosis and treatment of solid tumors. *Cancer Science*. 2003;94:315-320.

3. Nilsson B, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. *Cancer* 2005;103:821–9.

4. DeMatteo RP, Heinrich MC, El-Rifai WM, et al. Clinical management of gastrointestinal stromal tumors: before and after ST1-571. *Hum Pathol.* 2002;466-477.

5. Biswas S.K., Mantovani A. 2010. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat. Immunol.* 2010; 11: 889–896.

6. Cavnar MJ, Zeng S, Kim TS, et al. KIT oncogene inhibition drives intratumoral macrophage M2 polarization. *J Exp Med.* 2013;210:2873-2886.

7. Rusakiewicz S, Semeraro M, Sarabi M, et al. Immune infiltrates are prognostic factors in localized gastrointestinal tumors. *Cancer Res.* 2013;73:3499-3510.

8. Delahaye NF, Rusakiewicz S, Martins J, et al. Alternatively spliced NKp30 isoforms affect the prognosis of gastrointestinal stromal tumors. *Nat Med. 2011*;17:700-707.

9. Menard C, Blay JY, Borg C, et al. Natural killer cell IFN-gamma levels predict long-term survival with imatinib mesylate therapy in gastrointestinal stromal tumor-bearing patients. *Cancer Res.*2009;69:3563-3569.

10. Borg C, terme M, Taieb J, et al. Novel mode of action of c-kit tyrosine kinase inhibitors leading to NK cell-dependent antitumor effects. *J Clin Invest.* 2004;114:379-388.

11. Fernandez NC, et al. Dendritic cells (DC) promote natural killer (NK) cell functions: dynamics of the human DC/NK cell cross talk. *Nat. Med.* 1999;5:405–411.

12. Glas R, et al. Recruitment and activation of natural killer (NK) cells in vivo determined by the target cell phenotype. An adaptive component of NK cell-mediated responses. *J. Exp. Med.* 2000;191:129–138.

13. Balachandran VP, Cavnar MJ, Zeng S, et al. Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido. *Nat Med*.2011;17:1094–100.

14. Perez DR, Baser RE, Cavnar MJ, et al. Blood neutrophil-to-lymphocyte ratio is prognostic in gastrointestinal stromal tumor. *Ann Surg Oncol.* 2013;20:593-599.

15. Edris B, Willingham SB, Weiskopf K, et al. Anti-KIT monoclonal antibody inhibits imatinib-resistant gastrointestinal stromal tumor growth. *Proc Natl Acad Sci USA*; 2013;110:3501-3506.

16. Weiner LM, Surana R, Wang S. Monoclonal antibodies: Versatile platforms for cancer immunotherapy. *Nat Rev Immunol.* 2010;10(5):317–327.

17. Espinosa I, et al. A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. *Am J Surg Pathol.* 2008;32(2):210–218.

18. Matsumoto K, et al. Clinical efficacy and safety of sunitinib after imatinib failure in Japanese patients with gastrointestinal stromal tumor. *Jpn J Clin Oncol.* 2011;41(1):57–62.

19. Weiner LM, Surana R, Wang S. Monoclonal antibodies: Versatile platforms for cancer immunotherapy. *Nat Rev Immunol.* 2010;10(5):317–327.

20. Esposito I, et al. The stem cell factor-c-kit system and mast cells in human pancreatic cancer. *Lab Invest.* 2002;82(11):1481–1492.

21. Kemmer K, et al. KIT mutations are common in testicular seminomas. *Am J Pathol.* 2004;164(1):305.

22. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. *Nat Rev Cancer.* 2008;8:299–308.

23.Emtage PC, Lo AS, Gomes EM, Liu DL, Gonzalo-Daganzo RM, Junghans RP. Second-generation anti-carcinoembryonic antigen designer T cells resist activation-induced cell death, proliferate on tumor contact, secrete cytokines, and exhibit superior antitumor activity *in vivo*: a preclinical evaluation. *Clin Cancer Res.*2008;14:8112–8122.

24. Sadelain M, Riviere I, Brentjens R. Targeting tumours with genetically enhanced T lymphocytes. *Nat Rev Cancer.* 2003;3:35–45.

25. Schumacher TN. T-cell-receptor gene therapy. *Nat Rev Immunol.* 2002; 2:512–519.

26. Stauss HJ, Cesco-Gaspere M, Thomas S, Hart DP, Xue SA, Holler A, Wright G, Perro M, Little AM, Pospori C. Monoclonal T-cell receptors: new reagents for cancer therapy. *Mol Ther.* 2007;15:1744–1750.

27. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med.* 2011; 365:725–733.

28. Robbins PF, Morgan RA, Feldman SA,Wunderlich JR, Nahvi AV, Helman LJ, Mackall CL. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. *J Clin Oncol.* 2011;29:917–924.

29. Katz SC, Burga RA, Naheed S, et al. Anti-KIT designer T cells for the treatment of gastrointestinal stromal tumor. *J Trans Med.* 2013;11:46.

30. Kim TS, Cavnar MJ, Cohen NA, et al. Increased KIT inhibition enhances therapeutic efficacy in gastrointestinal stromal tumor. *Clin Cancer Res.* 2014;20:2350-2362.

31. Chen LL, Gouw L, Sabripour M, et al. Combining targeted therapy with immunotherapy (interferon-a): Rationale, efficacy in gastrointestinal stromal tumor model and implicatioons in other malignancies. *Oncoimmunol.* 2012; 1:773-776.

32. Chen LL, Chen X, Choi H, et al. Exploiting antitumor immunity to overcome relapse and improve remission duration. *Cancer Immunol Immunother.* 2011. [Epub ahead of print]. ■

Reassessing Risk and Prognostic Factors in GIST: Updated Histology Codes Redefine Epidemiology of the Disease

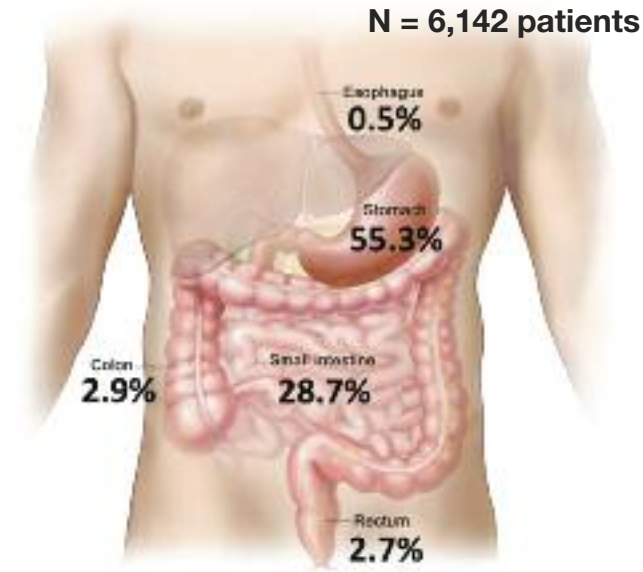
Jason K. Sicklick, MD, FACS
Assistant Professor of Surgery
Division of Surgical Oncology
Moores UCSD Cancer Center
University of California, San Diego
UC San Diego Health System
San Diego, California

Gastrointestinal stromal tumors (GIST) have emerged from what could be called the shadows of an earlier period when there was difficulty differentiating GIST from other submucosal gastrointestinal tumors and abdominal sarcomas. In turn, this led to widespread misdiagnoses and cancer registry miscoding. The incidence of GIST has long been underestimated and may still be underreported at many institutions. But since the adoption of a GIST-specific histology code, we can now better describe the epidemiology of this disease and identify patients at increased risk.

The new information is based on data compiled from SEER, the National Cancer Institute's Surveillance, Epidemiology, and End Results database.[1] In a recent study, our group identified 6,142 patients with histologically confirmed GIST between 2001 and 2011. The GI codes used were: C150-C189, C199, C209-C212, C218, C220-C221, C239-260, C268-C269, C480-C482, and C488. In contrast to earlier epidemiological reports, we also used the GIST-specific histology code ICD-O-3 code 8936, which was introduced in 2001. Using the SEER, we determined age-adjusted incidence rates per 100,000 subjects. Our multivariate analysis included age, sex, race, ethnicity, tumor site, tumor size, disease stage at diagnosis and year of diagnosis[2] (**Figure 1**).

The key findings can be summarized as follows:

- The annual incidence rate for the entire study period (2001-2011) was 0.68/100,000 and increased from 0.55/100,000 in 2001 to 0.78/100,000 in 2011. This most likely represents an increase in the application of the GIST ICD-O-3 code, rather than an actual rise in the incidence of disease (**Figure 2**).
- Annual incidence increased with age: the peak incidence was 3.06/100,000 for those 70-79 years of age. The median age at diagnosis was 64 years of age (**Figure 3**).
- GIST was 36% more common in men than woman and 23% more common in non-Hispanics than Hispanics.
- Blacks and Asians/Pacific Islanders were 2.07 and 1.50 times more likely to develop GIST than whites, respectively.
- The most common tumor sites were the stomach (55%) and small intestine (29%).



Tumor Site	Percent (%)
Peritoneum, Omentum and Mesentery	2.1
Retroperitoneum	0.9
Hepatopancreaticobiliary	0.4
Anus, Anal Canal and Anorectum	0.2
Gastrointestinal (Not Otherwise Specified)	6.3

Figure 1. The distribution of GIST at various sites.

Prognostic Factors

Among the more important findings from the study, we identified risk factors independently associated with worse overall survival (OS). These included increased age at diagnosis (hazard ratio [HR] 1.58), male sex (HR 1.41), black race (HR 1.26), and regional (HR 1.59) or metastatic (HR 2.81) disease at diagnosis. The factors that did not appear to be independently associated with worse OS were: ethnicity, tumor location, tumor size (>5 cm vs ≤2 cm), and earlier vs later diagnostic years.

(continued on page 112)

The Life Raft GROUP

PATIENT ADVOCACY

INNOVATIVE. EFFICIENT. COLLABORATIVE. EFFECTIVE.

THE LIFE RAFT GROUP is a non-profit with a simple focus: to cure a form of cancer – GIST (gastrointestinal stromal tumor) – and to help those living with it until then. To achieve this, we focus on three key areas: Patient Support & Education, Advocacy, & Research.

PATIENT SUPPORT & EDUCATION

- Newsletters
- Website, Social Media, Mobile Apps
- Educational videos and webcasts
- Clinical Trials Database
- Life Fest and GIST Day of Learning
- LRG Email Community
- Local Groups and Sister Organizations across the US and Internationally

ADVOCACY

- Fight placebos in clinical trials
- Advocate in support of legislative issues affecting the GIST community
- Help patients access effective treatments
- Advocate for mutational testing and plasma level testing

RESEARCH

- Research Team: An innovative approach making the research process move faster and more efficiently
- Patient Registry
- GIST Collaborative Tissue Bank

CONTACT US

155 US Highway 46, Suite 202
Wayne, NJ 07470

973-837-9092
liferaft@liferaftgroup.org

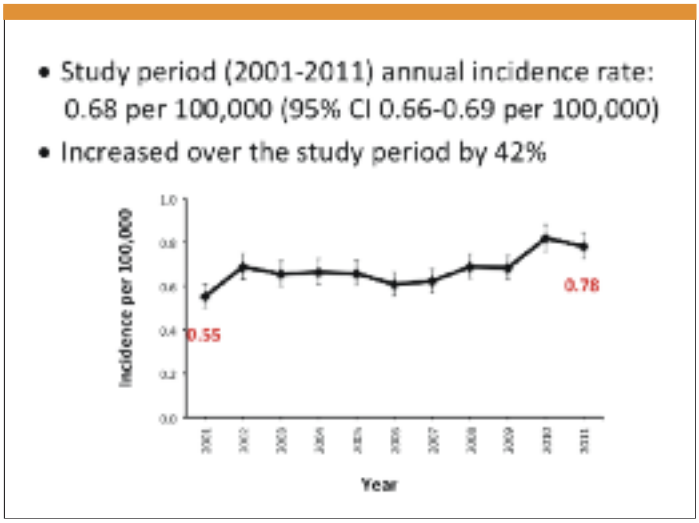


Figure 2. Annual incidence rate.

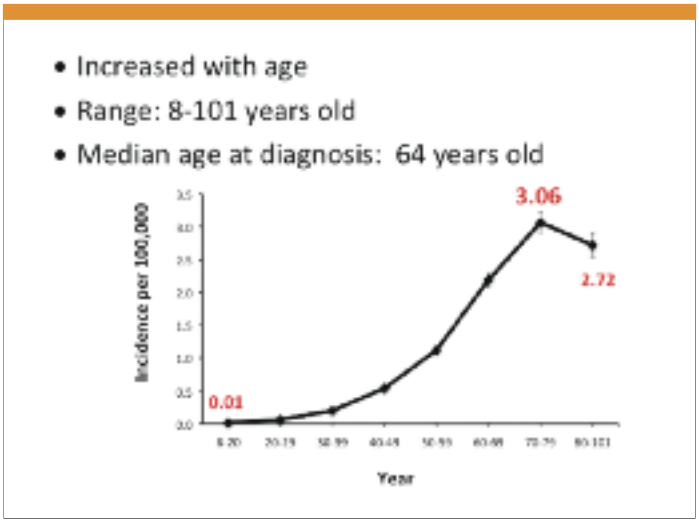
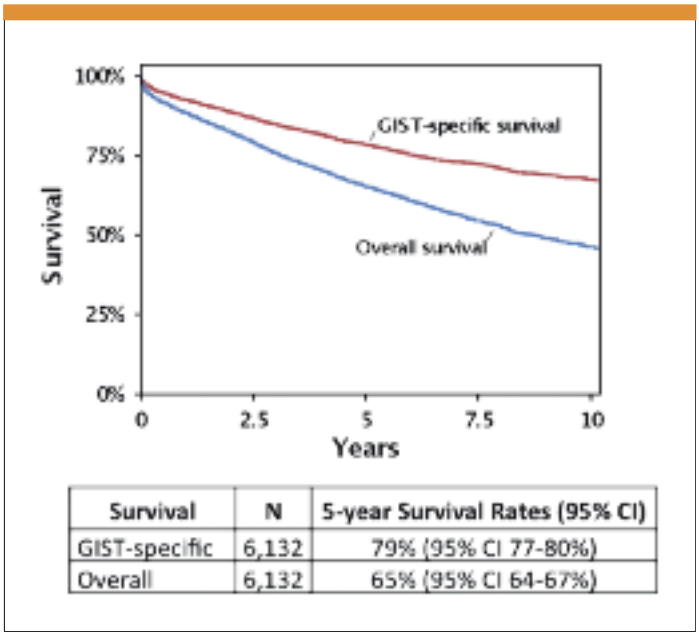


Figure 3. Annual incidence rate.

The independent predictors of worse GIST-specific survival were similar to those for OS. These included increased age at diagnosis, male sex, black race, and regional/ metastatic disease at diagnosis. Additionally, earlier vs. later diagnostic years was associated with a worse GIST-specific mortality. On the other hand, location of the tumor and tumor size were not significantly associated with GIST-specific survival.

While the results from our analysis corroborated some earlier findings, they also contradicted several. For instance, previous findings have shown that tumor size was a significant predictor of GIST-specific survival. However, we found that tumors larger than 5 cm were not associated with worse GIST-specific survival than tumors smaller than 2 cm. Tumors located in the small intestines were also not found to be associated with worse prognosis as opposed to those in the stomach. Furthermore, we found that the 5-year OS rate (65%) was higher than previous studies (**Figure 4**). These findings are probably attributable, as least in part, to the introduction of imatinib in 2001 which had allowed surgeons to perform to be more aggressive in their approaches since we noted improvements in GIST-specific survival in the later years of the study (2004-2011), but this trend had no effect on overall survival.

In summary, this study represents the first population-based assessment of GIST epidemiology in the U.S. using ICD-O-3 coding. In its comprehensive description and statistical examination, it offers a perspective on GIST enhanced by the modern era of immunohistochemical diagnoses. The data supports some findings from earlier reports, but it markedly differs in other respects. By reducing pathologic and coding confounders that had limited the accuracy of previous SEER-based reports, our findings more realistically reflect the present-day incidence (6.8 cases per million people per year) of GIST in the U.S. Our findings also agreed with other reports with respect to GIST being more common in males and blacks. However, the finding in Asians/Pacific Islanders is novel in the U.S., but consistent with the much higher age-adjusted incidence of 19.7 cases per million people per year found in a study from Taiwan.[3] In conclusion,



Survival	N	5-year Survival Rates (95% CI)
GIST-specific	6,132	79% (95% CI 77-80%)
Overall	6,132	65% (95% CI 64-67%)

Figure 4. Survival rates in GIST patients.

much remains to be elucidated about the epidemiology of GIST, including explanations for the racial and ethnic differences noted in the incidence and survival of these patients.

References

1. Surveillance, Epidemiology, and End Results (SEER) Program (http://www.seer.cancer.gov) seer Stat Database: Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (2000-2011) <Katrina/Rita Population Adjustment>Linked to County Attributes-Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014 (updated 5/7/2014) based on the November 2013 submission.
2. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of Gastrointestinal Stromal Tumors in the Era of Histology Codes: Results of a Population-Based Study. *Cancer Epidemiol Biomarkers Prev cebp.1002.2014; Published OnlineFirst October 2, 2014; doi:10.1158/1055-9965.EPI-14-1002*
3. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. *Am J Gastroenterol.* 2005;100:162-168. ■

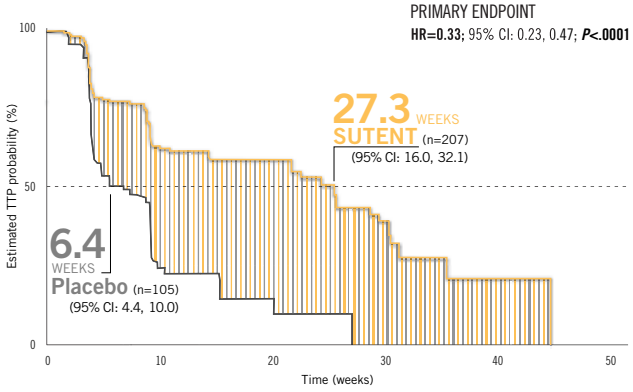
SUTENT® (sunitinib malate) is indicated for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate.

With a 4-fold increase in median TTP in imatinib-resistant or -intolerant GIST...

THIS IS NOT JUST ANOTHER SUNDAY. IT'S ANOTHER SUNDAY.

In the phase 3, randomized, double-blind, placebo-controlled trial in imatinib-resistant or -intolerant GIST (N=312)...

4-fold increase in median TTP and 67% reduced risk of progression



SUTENT is the only 2nd-line therapy for patients with imatinib-resistant or -intolerant GIST

Duration of median PFS (secondary endpoint) was consistent with median TTP

- Significant improvement in PFS (HR=0.33 [95% CI: 0.24, 0.47; *P*<.0001])
  - Median: 24.1 weeks (5.6 months) for SUTENT vs 6 weeks (1.4 months) with placebo (95% CI: 11.1, 28.3 and 4.4, 9.9, respectively)

According to the National Comprehensive Cancer Network® (NCCN®), sunitinib malate (SUTENT®) is the category 1–recommended 2nd-line TKI for GIST treatment[1]

- For patients with limited or widespread disease progression on the standard dose of imatinib, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.2.2014 recommend dose escalation of imatinib as tolerated or changing to sunitinib malate (SUTENT®)[1]

Data are from the phase 3, multicenter, double-blind, placebo-controlled study, in which 312 patients with imatinib-resistant or -intolerant GIST were randomized 2:1 to receive either SUTENT or placebo. Patients were treated with either 50-mg SUTENT once daily in cycles of 4 weeks on/2 weeks off or placebo. The primary endpoint was time to tumor progression.

Important Safety Information

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Given the potential for serious adverse reactions (ARs) in nursing infants, a decision should be made whether to discontinue nursing or SUTENT.

Cardiovascular events, including heart failure, myocardial disorders, and cardiomyopathy, some of which were fatal, have been reported. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.

SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including torsades de pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Hypertension may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS).

Hemorrhagic events, including tumor-related hemorrhage such as pulmonary hemorrhage, have occurred. Some of these events were fatal. Perform serial complete blood counts (CBCs) and physical examinations.

Osteonecrosis of the jaw (ONJ) has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving bisphosphonates.

Cases of tumor lysis syndrome (TLS) have been reported primarily in patients with high tumor burden. Monitor these patients closely and treat as clinically indicated.

Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, and treat per standard medical practice.

Cases of impaired wound healing have been reported. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures.

Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose-reduce if 24-hour urine protein is ≥3 g; discontinue SUTENT in cases of nephrotic syndrome or repeat episodes of urine protein ≥3 g despite dose reductions.

Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, treatment must not be re-started.

Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.

CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Dose adjustments are recommended when administered with CYP3A4 inhibitors or inducers.

The most common ARs occurring in ≥20% of patients with GIST and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (40% vs 27%), anorexia (33% vs 29%), skin discoloration (30% vs 23%), mucositis/stomatitis (29% vs 18%), asthenia (22% vs 11%), altered taste (21% vs 12%), and constipation (20% vs 14%). The most common grade 3/4 ARs (occurring in ≥4% of patients with GIST receiving SUTENT vs placebo) were asthenia (5% vs 3%), hand-foot syndrome (4% vs 3%), diarrhea (4% vs 0%), and hypertension (4% vs 0%).

The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with GIST receiving SUTENT vs placebo) included lipase (10% vs 7%), neutrophils (10% vs 0%), amylase (5% vs 3%), and platelets (5% vs 0%).

Please see Brief Summary, including Boxed Warning, on the following 3 pages.

capsules
SUTENT®
sunitinib malate

Evidence. Experience. Every Day.

SUTENT® (SUNITINIB MALATE) CAPSULES, ORAL

Brief Summary of Prescribing Information

WARNING: HEPATOTOXICITY

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. *[See Warnings and Precautions]*

INDICATION AND USAGE: Gastrointestinal Stromal Tumor (GIST) SUTENT is indicated for the treatment of GIST after disease progression on or intolerance to imatinib mesylate.

DOSAGE AND ADMINISTRATION

Recommended Dose. The recommended dose of SUTENT for GIST is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).

Dose Modification. Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability. A dose reduction for SUTENT to a minimum of 37.5 mg daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor *[see Drug Interactions]*. A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity *[see Drug Interactions]*.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Safety in patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN has not been established.

Pregnancy. SUTENT can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Left Ventricular Dysfunction

In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Cardiovascular events, including heart failure, myocardial disorders and cardiomyopathy, some of which were fatal, have been reported through post-marketing experience. For GIST, more patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving placebo. In the double-blind treatment phase of GIST Study A, 22/209 patients (11%) on SUTENT and 3/102 patients (3%) on placebo had treatment-emergent LVEF values below the lower limit of normal (LLN). Nine of 22 GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction: one patient; addition of antihypertensive or diuretic medications: four patients). Six patients went off study without documented recovery. Additionally, three patients on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF <40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In the double-blind treatment phase of GIST Study A, 1 patient on SUTENT and 1 patient on placebo died of diagnosed heart failure; 2 patients on SUTENT and 2 patients on placebo died of treatment-emergent cardiac arrest.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

QT Interval Prolongation and Torsade de Pointes. SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered *[see Dosage and Administration]*.

Hypertension. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

While all-grade hypertension was similar in GIST patients on SUTENT compared to placebo, Grade 3 hypertension was reported in 9/202 GIST patients on SUTENT (4%), and none of the GIST patients on placebo. No GIST patients discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 8/202 GIST patients on SUTENT (4%) and 1/102 GIST patients on placebo (1%).

Hemorrhagic Events. Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. Bleeding events occurred in 37/202 patients (18%) receiving SUTENT in the double-blind treatment phase of GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. In the double-blind treatment phase of GIST Study A, 14/202 patients (7%) receiving SUTENT and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in GIST Study A taking placebo had a fatal gastrointestinal bleeding event during Cycle 2.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Cases of pulmonary hemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with SUTENT. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5/202 patients (3%) with GIST receiving SUTENT on Study A. Tumor hemorrhages were observed as early as Cycle 1 and as late as Cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrhage. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Osteonecrosis of the Jaw (ONJ). ONJ has been observed in clinical trials and has been reported in post-marketing experience in patients treated with SUTENT. Concomitant exposure to other risk factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw.

Tumor Lysis Syndrome (TLS). Cases of TLS, some fatal, have occurred in patients treated with SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

Thyroid Dysfunction. Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, on SUTENT treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Treatment-emergent acquired hypothyroidism was noted in eight GIST patients (4%) on SUTENT versus one (1%) on placebo.

Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

Wound Healing. Cases of impaired wound healing have been reported during SUTENT therapy. Temporary interruption of SUTENT therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Proteinuria. Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalyses during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose-reduce for 24-hour urine protein ≥3 g. Discontinue SUTENT in patients with nephrotic syndrome or repeat episodes of urine protein ≥3 g despite dose reductions. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

Dermatologic Toxicities. Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of SJS, TEN, or EM (eg, progressive skin rash, often with blisters or mucosal lesions) are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, SUTENT treatment must not be restarted.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with SUTENT, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

Adrenal Function. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Laboratory Tests. CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 660 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of GIST, an active-controlled trial (n=375) for the treatment of renal cell carcinoma (RCC) or a placebo-controlled trial (n=83) for the treatment of pNET. The GIST patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.

The most common adverse reactions (≥20%) in patients with GIST, RCC or pNET are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in *Warnings and Precautions*. Other adverse reactions occurring in GIST Study A are described below.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in GIST Study A. Median duration of blinded study treatment was two cycles for patients on SUTENT (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6) for patients on placebo at the time of the interim analysis. Dose reductions occurred in 23 patients (11%) on SUTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT and 31 patients (30%) on placebo. The rates of treatment-emergent, non-fatal adverse reactions resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 56% versus 51% of patients

on SUTENT versus placebo, respectively, in the double-blind treatment phase of the trial.

The following table compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT and reported more commonly in patients receiving SUTENT than in patients receiving placebo.

Adverse Reactions Reported in Study A in at Least 10% of GIST Patients who Received SUTENT in the Double-Blind Treatment Phase and More Commonly Than in Patients Given Placebo*

Adverse Reaction, n (%)	SUTENT (n=202)		Placebo (n=102)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any		114 (56)		52 (51)
Gastrointestinal				
Diarrhea	81 (40)	9 (4)	27 (27)	0 (0)
Mucositis/stomatitis	58 (29)	2 (1)	18 (18)	2 (2)
Constipation	41 (20)	0 (0)	14 (14)	2 (2)
Cardiac				
Hypertension	31 (15)	9 (4)	11 (11)	0 (0)
Dermatology				
Skin discoloration	61 (30)	0 (0)	23 (23)	0 (0)
Rash	28 (14)	2 (1)	9 (9)	0 (0)
Hand-foot syndrome	28 (14)	9 (4)	10 (10)	3 (3)
Neurology				
Altered taste	42 (21)	0 (0)	12 (12)	0 (0)
Musculoskeletal				
Myalgia/limb pain	28 (14)	1 (1)	9 (9)	1 (1)
Metabolism/ Nutrition				
Anorexia[a]	67 (33)	1 (1)	30 (29)	5 (5)
Asthenia	45 (22)	10 (5)	11 (11)	3 (3)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0

[a]Includes decreased appetite

In the double-blind treatment phase of GIST Study A, oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on SUTENT versus 3 (3%) on placebo. Hair color changes occurred in 15 patients (7%) on SUTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUTENT versus 2 (2%) on placebo.

The following table provides common (≥10%) treatment-emergent laboratory abnormalities.

Laboratory Abnormalities Reported in Study A in at Least 10% of GIST Patients Who Received SUTENT or Placebo in the Double-Blind Treatment Phase*

Laboratory Parameter, n (%)	SUTENT (n=202)		Placebo (n=102)	
	All Grades*	Grade 3/4*[a]	All Grades*	Grade 3/4*[b]
Any		68 (34)		22 (22)
Gastrointestinal				
AST / ALT	78 (39)	3 (2)	23 (23)	1 (1)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Total bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Cardiac				
Decreased LVEF	22 (11)	2 (1)	3 (3)	0 (0)
Renal/Metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Potassium decreased	24 (12)	1 (1)	4 (4)	0 (0)
Sodium increased	20 (10)	0 (0)	4 (4)	1 (1)
Hematology				
Neutrophils	107 (53)	20 (10)	4 (4)	0 (0)
Lymphocytes	76 (38)	0 (0)	16 (16)	0 (0)
Platelets	76 (38)	10 (5)	4 (4)	0 (0)
Hemoglobin	52 (26)	6 (3)	22 (22)	2 (2)

LVEF=Left ventricular ejection fraction

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0

[a]Grade 4 laboratory abnormalities in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), potassium decreased (1%), neutrophils (2%), hemoglobin (2%), and platelets (1%).

[b]Grade 4 laboratory abnormalities in patients on placebo included amylase (1%), lipase (1%) and hemoglobin (2%).

After an interim analysis, the study was unblinded, and patients on the placebo arm were given the opportunity to receive open-label SUTENT treatment. For 241 patients randomized to the SUTENT arm, including 139 who received SUTENT in both the double-blind and open-label treatment phases, the median duration of SUTENT treatment was 6 cycles (mean 8.5, range 1 – 44). For the 255 patients who ultimately received open-label SUTENT treatment, median duration of study treatment was 6 cycles (mean 7.8, range 1 – 37) from the time of the unblinding. A total of 118 patients (46%) required dosing interruptions, and a total of 72 patients (28%) required dose reductions. The incidence of treatment-emergent adverse reactions resulting in permanent discontinuation was 20%. The most common Grade 3 or 4 treatment-related adverse reactions experienced by patients receiving SUTENT in the open-label treatment phase were fatigue (10%), hypertension (8%), asthenia (5%), diarrhea (5%), hand-foot syndrome (5%), nausea (4%), abdominal pain (3%), anorexia (3%), mucositis (2%), vomiting (2%), and hypothyroidism (2%).

Venous Thromboembolic Events. Seven patients (3%) on SUTENT and none on placebo in the double-blind treatment phase of GIST Study A experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT), and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Reversible Posterior Leukoencephalopathy Syndrome. There have been reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Pancreatic and Hepatic Function. If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Hepatotoxicity was observed in patients receiving SUTENT *[see Boxed Warning and Warnings and Precautions]*.

Post-marketing Experience. The following adverse reactions have been identified during post-approval use of SUTENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: thrombotic microangiopathy; hemorrhage associated with thrombocytopenia*. Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Hepatobiliary disorders: cholecystitis, particularly acalculous cholecystitis.

Gastrointestinal disorders: esophagitis.

Immune system disorders: hypersensitivity reactions, including angioedema.

Infections and infestations: serious infection (with or without neutropenia)*; necrotizing fasciitis, including of the perineum*. The infections most commonly observed with sunitinib treatment include respiratory, urinary tract, skin infections and sepsis/septic shock.

Musculoskeletal and connective tissue disorders: fistula formation, sometimes associated with tumor necrosis and/or regression*; myopathy and/or rhabdomyolysis with or without acute renal failure*. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Renal and urinary disorders: renal impairment and/or failure*; proteinuria; rare cases of nephrotic syndrome. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome.

Respiratory disorders: pulmonary embolism.*

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, including positive dechallenges; erythema multiforme and Stevens-Johnson syndrome.

Vascular disorders: arterial thromboembolic events*. The most frequent events included cerebrovascular accident, transient ischemic attack and cerebral infarction.

*including some fatalities

DRUG INTERACTIONS/CYP3A4 Inhibitors. Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors *[see Dosage and Administration]*.

CYP3A4 Inducers. CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers *[see Dosage and Administration]*.

In Vitro Studies of CYP Inhibition and Induction. *In vitro* studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category D *[see Warnings and Precautions]*.

Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at doses ≥1 mg/kg/day but no maternal reproductive toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). At the high dose of 3 mg/kg/day, reduced body weights were observed at birth and persisted for offspring of both sexes during the pre-weaning period and in males during post-weaning period. No other developmental toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Nursing Mothers. Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether this drug or its primary active metabolite are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SUTENT, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use. The safety and efficacy of SUTENT in pediatric patients have not been established.

Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were > 0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of

physeal dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

Geriatric Use. Of 825 GIST and RCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

Hepatic Impairment. No dose adjustment to the starting dose is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

Renal Impairment. No adjustment to the starting dose is required when administering SUTENT to patients with mild, moderate, and severe renal impairment. Subsequent dose modifications should be based on safety and tolerability *[see Dose Modification]*. In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to subjects with normal renal function, the sunitinib exposure is 47% lower in subjects with ESRD on hemodialysis. Therefore, the subsequent doses may be increased gradually up to 2 fold based on safety and tolerability.

OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. A few cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT, or without adverse reactions. A case of intentional overdose involving the ingestion of 1,500 mg of SUTENT in an attempted suicide was reported without adverse reaction. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility. The carcinogenic potential of sunitinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. There were similar positive findings in both species. In rasH2 transgenic mice gastroduodenal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiosarcomas were observed at doses of ≥25 mg/kg/day following daily dose administration of sunitinib in studies of 1- or 6-months duration. No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day. Similarly, in a 2-year rat carcinogenicity study, administration of sunitinib in 28-day cycles followed by 7-day dose-free periods resulted in findings of duodenal carcinoma at doses as low as 1 mg/kg/day (approximately 0.9 times the AUC in patients given the RDD of 50 mg/day). At the high dose of 3 mg/kg/day (approximately 7.8 times the AUC in patients at the RDD of 50 mg/day) the incidence of duodenal tumors was increased and was accompanied by findings of gastric mucous cell hyperplasia and by an increased incidence of pheochromocytoma and hyperplasia of the adrenal medulla. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (≥5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (≥0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6 mg/kg dose produced a mean AUC that was ≥0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was ≥5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10 mg/kg/day dose produced a mean AUC that was ≥25.8 times the AUC in patients administered the RDD).

PATIENT COUNSELING INFORMATION

Gastrointestinal Disorders. Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

Skin Effects. Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

Other Common Events. Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Musculoskeletal Disorders. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients being treated with SUTENT, who have previously received or are receiving bisphosphonates, invasive dental procedures should be avoided, if possible.

Concomitant Medications. Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Drug Interactions]*.

Rx only Revised: June 2014

GIST Investigator Highlights Key Trends in Epidemiology of the Disease

This interview was conducted with Jason K. Sicklick, MD, FACS, from the Division of Surgical Oncology and Department of Surgery, Moores Cancer Center, University of California, San Diego. Dr. Sicklick is the senior author of a recent publication in the journal, Cancer Epidemiology, Biomarkers and Prevention.

Q. What do you consider the most important change in reclassifying and recoding gastrointestinal stromal tumors (GIST) in the last 10-15 years?

Dr. Sicklick: Historically, GIST and non-GIST histologies were lumped together in US epidemiological studies reporting on GIST. As a result, other tumors, like leiomyosarcoma, were included in the data analyses and confounded the results. With the discovery of c-KIT (CD117) immunohistochemical staining to diagnose the majority of GIST, pathologists can now histologically distinguish this disease from others. Now, GIST can be coded in cancer databases as a separate entity from other tumors. Therefore, the biggest change from previous studies, and probably the most important one, is excluding all other tumor types from our analyses in order to have a purer population of GIST patients to study.

Q. On a practical basis, and in the clinical setting, how have these changes been implemented in terms of coding?

Dr. Sicklick: When a tumor is removed and goes to the pathology lab, pathologists are aware of the differences in GIST versus the other tumors. Once the diagnosis is made, the final pathology report is inserted into the medical record. Subsequently, cancer registrars at each institution assign the GIST code to a given patient's tumor and this data, as well as additional information about their demographics and tumor are submitted to the national cancer registry. Before 2001, there was a code that was simply "GI sarcoma." Initially, a registrar who did not know the difference between a leiomyosarcoma and GIST would assign the tumor this "wastebasket diagnosis code." However, with increased knowledge and education, the application of a new code specific to GIST has become increasingly utilized. As a result, we can now query the databases in a more fine tuned manner.

Q.. Are we capturing all of the GIST cases now?

Dr. Sicklick: Probably not because there is one caveat. There is no code for "benign" versus malignant GIST. Theoretically, we might still be underestimating a subset of GIST. Only those coded as malignancies end up in the SEER database. As a result, GIST is probably more common than we appreciate.

"There is no code for 'benign' versus malignant GIST. Theoretically, we might still be underestimating a subset of GIST. Only those coded as malignancies end up in the SEER database. As a result, GIST is probably more common than we appreciate."

Q. How is the SEER database different from other databases?

Dr. Sicklick: The practical importance is that it represents a broad view of GIST across the United States because SEER represents 28% of all U.S. cancer patients. While not 100%, we are gaining insight from many geographical regions and many institutions. Furthermore, the data is not based upon individuals volunteering data or self-reporting. Finally, when the coders do report the data, they are subject to random checks and external audits to ensure increased accuracy of the data. While no system is perfect, this method works pretty well to provide us with a view of US cancer epidemiology and trends.

Q. What would you say accounts for the higher incidence of GIST among African Americans and Asian/Pacific Islanders in your report?

Dr. Sicklick: The association with African Americans has been reported before. I have the same question. We do not have an answer yet—could it be diet, infectious, toxin exposure, genetics, or other factors? I wish I had an answer. There is no way to glean that information from our data and we need more epidemiological investigations to delve into

such risk factors. Practicing in Southern California, I anecdotally noticed that a lot of my GIST patients were of Chinese or Taiwanese decent. But, my colleagues and I attributed this to demographics particular to our patient population. However, our findings supported my hunch. Interestingly, there was a report from a group in Taiwan reported an incidence of GIST that is almost 3 times the overall incidence rate that we reported in the US Perhaps enriching for such a population may explain this. Again, we do not have an answer as to why this could be, but if we can figure out underlying risk factors for developing GIST, that would be a huge finding.

Q. It would seem intuitive that the improved GIST-specific survival you observed would be attributed to the use of imatinib, including in the metastatic setting, correct?

Dr. Sicklick: Yes, the survival is better and we can probably attribute this to the use of imatinib. In fact, 25% of GIST patients with metastatic disease are still alive at 10 years after diagnosis. However, our data does not directly address this question. A study using the SEER-Medicare database could answer this question because medication use can be studied with it. However, this database only captures individuals ≥ 65 years old. Thus, more than half of patients would be automatically excluded from such an analysis. This is less than ideal. A second point to make is that GIST often has a less aggressive disease biology than tumors like leiomyosarcoma. By filtering out these patients, the survival was also likely improved.

Q. So, overall, what are the primary risk factors in the 5-year survival data?

Dr. Sicklick: The primary determinants of overall survival are age, gender, race, and tumor stage. Tumor size and location were not risk factors.

Q. Are there a few take-home messages from the new data in terms of diagnosis and prognosis?

Dr. Sicklick: Our knowledge about GIST biology, genomics, treatments and even epidemiology continue to evolve. While GIST is a "rare disease" as compared to many other cancers, if it affects a patient or a loved one, it is common. It is a disease that should be cared for by an experienced, multidisciplinary team. Our data points to the fact that it should be a disease that every primary care physician, gastroenterologist, surgeon, and medical oncologist is aware of. Moreover, the index of suspicion should be heightened in higher risk patient populations, such as African Americans and Asian/Pacific Islanders. While the survival rates are not different between Asians and Caucasians, a difference remains between African Americans and Caucasians. This health care disparity gap needs to be further investigated, bridged and closed. ■

"Our data points to the fact that it should be a disease that every primary care physician, gastroenterologist, surgeon, and medical oncologist is aware of. Moreover, the index of suspicion should be heightened in higher risk patient populations, such as African Americans and Asian/Pacific Islanders."

Managing Side Effects of TKI Treatment: Duration of Therapy in the Face of Toxicity

Lori Williams, MSN, PhD
Assistant Professor,
Symptom Research CAO
The University of Texas
MD Anderson Cancer Center
Houston, Texas

This is the second of a two-part series on side effects associated with tyrosine kinase inhibitor (TKI) therapy. It presents practical strategies to prolong TKI treatment and maintain therapeutic levels of these agents.

As management options for gastrointestinal stromal tumor (GIST) have expanded over the last few years, the treatment algorithm for the disease is being reconsidered and to some extent revised, incorporating new perspectives gained not only from the prolonged use of imatinib but from the use of second- and third-line agents. As knowledge of tyrosine kinase inhibitors (TKIs) is gained, the issue of management of adverse effects is beginning to receive the attention it deserves. Despite the need for a greater focus, there is not a wealth of evidence to guide clinical decision making. Unfortunately, relatively little systematic research has been conducted on the management of TKI-related toxicities.[1] There are anecdotal reports, some case reports, and an effort by at least one group to identify prognostic factors and calculate a predictive score for toxicity to treatment with imatinib, such as periorbital edema (**Figure 1**).[2]

There are signs, however, that the issue is being addressed with a more systematic approach, suggesting that effective management may be moving from an often empirical to a more evidence-based approach, increasing the likelihood of maintaining optimal drug levels. The addition of new agents (sunitinib and regorafenib) has provided an impetus to review side effect management and this trend is likely to grow stronger in view of several next-generation TKIs and combination regimens currently in various stages of development.[1] These include nilotinib, masitinib, dasatinib, sorafenib, and imatinib in combination with everolimus and vatalinib.

Because TKIs are often administered for prolonged periods of time, a crucial factor, especially for patients, is the effective management of side effects. Even low-grade side effects that persist for extended periods can impact patients' ability to function as they would like. In addition, side effects may interfere with patient compliance with treatment medication, which is a prime concern in the effectiveness of TKIs. For example, discontinuation of imatinib administration results in a rapid tumor progression in the majority of patients with advanced GIST and low imatinib plasma concentrations (<1100 ng/mL) are associated with a short time to disease progression.[3]

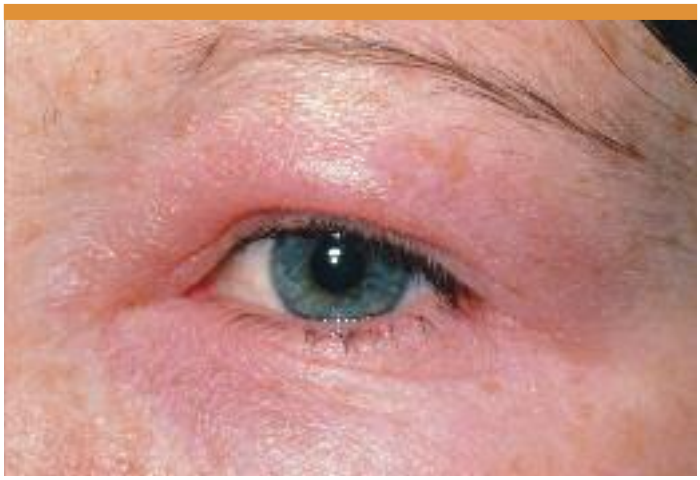


Figure 1. Patient's eye with swelling, as a side effect to imatinib treatment. The eyelids are puffy and red, with a fluid swelling (periorbital edema) around the eye.

Managing Non-hematological Side Effects

Hand-foot Syndrome

Numerous studies document that hand-foot skin effects are among the most frequent reasons for dose alterations.[4-7] This adverse effect has been reported in 13.5 to 25% of GIST patients on sunitinib. However, it is extremely rare in patients receiving imatinib. Typically symptoms occur with repeated sunitinib treatment and within 2 to 4 weeks of when the drug is first administered. Unlike the classical hand-foot skin reaction (**Figures 2** and **3**) associated with chemotherapy, palmar-plantar erythrodysesthesia (PPE) induced by TKIs is more localized and hyperkeratotic. This re-

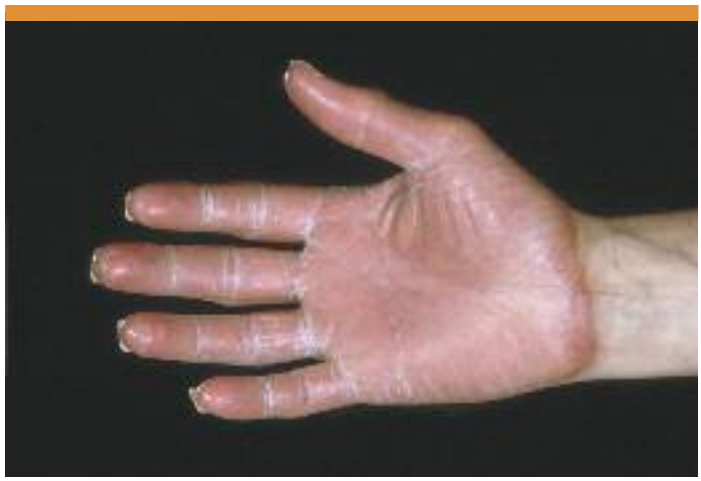


Figure 2. Hand-Foot Syndrome on hand, palmar, as a result of TKI treatment. Also called palmar-plantar erythrodysesthesia or acral erythema.

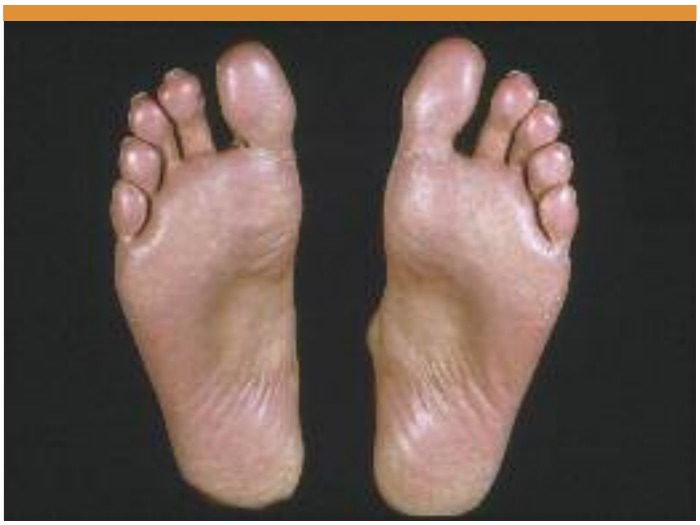


Figure 3. Hand-Foot Syndrome on soles of feet, as a result of TKI treatment. Also called palmar-plantar erythrodysesthesia or acral erythema.

action may be related to poor repair of repeated small traumas in hands and feet due to the VEGFR- and PDGFR-inhibiting activity of sunitinib and to direct skin toxicity of the drug.

Management. As is the case with many side effects, the cornerstone of managing hand-foot syndrome remains patient education, early identification of symptoms, and proactive management to avoid severe and debilitating progression. In educating the patient, nurses play a vital role, counseling patients on the expected duration and nature of the associated symptoms or syndrome. A 2-week suspension of the drug tends to facilitate a rapid improvement in symptoms of the hand-foot skin reaction. The patient may also benefit from an early referral to a podiatrist, even before sunitinib is initiated.[1]

Nevertheless, management of hand-foot skin reaction is empirical, and interruption of therapy is the accepted approach. These principles apply:

- When a hand-foot skin reaction is painful and interferes with daily activities, treatment interruption or dose reduction may be necessary until symptoms abate to Grade 1.
- Analgesics may be appropriate to ameliorate pain. Trauma and extreme temperatures should be avoided; patients should be advised about the use of pressure-absorbing insoles and comfortable shoes or gloves.[1]

Skin Rash

Affecting up to one-third of GIST patients receiving imatinib and 15% of those on sunitinib, skin rash is also among the most frequent of adverse effects.[8-11] There is a linear relationship between incidence of this side effect and escalating doses of imatinib; 46.6% of those treated with 800 mg/day develop rash. Patients on imatinib commonly present with erythematous, maculopapular lesions, appearing during the first weeks of treatment; the forearms are a frequent site of the rash. An estimated 16% of patients receiving sunitinib may develop dry skin. Sunitinib causes inflammatory follicular papules on the face and/or trunk.

Management. The options include the following: topical lotions for rough skin and antihistamines, topical lotions, or topical steroids for patients with mild to moderate skin reactions with imatinib. Interruptions in treatment or reductions in dose for more severe cases are appropriate as well as initiation of systemic steroids (prednisone 1 mg/kg, tapered as rash improves to 20 mg/day), at which point imatinib can be reintroduced.[1]

"Affecting up to one-third of GIST patients receiving imatinib and 15% of those on sunitinib, skin rash is also among the most frequent of adverse effects.7-10 There is a linear relationship between incidence of this side effect with escalating doses of imatinib; 46.6% of those treated with 800 mg/day develop rash. "

Skin and Hair Discoloration

Skin discoloration is primarily associated with the use of sunitinib (in approximately 25% of patients) and is characterized by yellowish skin or hypo- or hyperpigmentation. The side effect is believed to be the result of the drug itself (a yellow to orange powder). Inhibition of KIT signaling reduces hair pigmentation and the functioning of tyrosinase and tyrosinase-related protein 1 involved in melanin synthesis.[12,13]

Management. In the case of sunitinib-related effects, patients can be advised that the changes are self-limiting and resolve within a few weeks of the time the drug is discontinued.

Mucositis and Stomatitis

A complex of symptoms, including mouth pain, a burning sensation when eating acidic or highly spiced foods or difficulty with speech or swallowing have been observed in 16 to 21% of GIST patients on sunitinib. These problems, involving mucositis, are generally not seen with imatinib.[1]

Management. Because the symptoms are generally mild to moderate, dose modification can usually be avoided. Advice on oral hygiene and use of mouth rinses such as sodium bicarbonate, as well as topical or systemic analgesics are one

Table. Examples of results for individual patients

Patients' characteristics						Dose (mg/d)	Probability of grade 2 (or higher) toxicity (%)				
Age (years)	Sex	PS (WHO)	Prior Chemotherapy	Lesion size (mm)	GI Origin		Oedema	Fatigue	Skin rash	Nausea	Diarrhea
(a) Non-hematological toxicities											
60	M	1	No	80	Yes	400	18	24	9	9	14
						800	39	44	21	21	21
40	M	1	No	80	Yes	400	13	18	5	9	14
						800	31	36	12	21	21
75	M	1	No	80	Yes	400	22	29	15	9	14
						800	46	51	31	21	21
60	F	1	No	80	Yes	400	32	24	9	21	20
						800	58	44	21	40	29
60	M	0	No	80	Yes	400	18	18	9	6	14
						800	39	36	21	15	21
60	M	2	No	80	Yes	400	18	30	9	13	14
						800	39	52	21	28	21
60	M	1	Yes	80	Yes	400	18	34	9	9	14
						800	39	57	21	21	21
60	M	1	No	25	Yes	400	18	24	13	9	14
						800	39	44	28	21	21
60	M	1	No	200	Yes	400	18	24	5	9	14
						800	39	44	11	21	21
60	M	1	No	80	No	400	18	24	9	9	7
						800	39	44	21	21	11

Patients' characteristics		Dose (mg/d)	Probability of grade 3 (or 4) toxicity (%)	
HGB (mmol/l)	ANC (10**9/1)		Anemia	Neutropenia
(b) Hematological toxicities				
8	5	400	6	6
		800	14	6
6	5	400	20	12
		800	41	12
9	5	400	3	4
		800	8	4
8	3	400	6	1
		800	14	11
8	9	400	6	2
		800	14	2

PS (WHO), World Health Organization performance score. ANC, absolute neutrophil count; HGB, hemoglobin level.

This predictive model suggests the probability of various side effects based on dose of imatinib and patient characteristics.[2]

of the keys to management. Avoidance of irritating foods is another important strategy to minimizing the impact of this side effect. In severe cases, dose interruption or dose reduction may be needed but tend to be rare.[1]

Nausea and Vomiting

Both imatinib and sunitinib are associated with nausea and vomiting. More than 49% of patients on imatinib and more than 37% of patients on sunitinib report nausea and vomiting, but only 1-3% or patients on imatinib and 3.4% of patients on sunitinib report severe Grade 3 and 4 nausea and vomiting. A dose relationship with nausea and vomiting is observed with imatinib, especially when the drug is taken on an empty stomach.[1]

Management. The most important strategies to avoid this side effect are to ensure that imatinib is taken with food, preferably with the largest meal of the day,[14,15] or to split the dose and take the medication with different meals. In severe cases, antiemetic medications such as ondansetron are beneficial. Because side effects with imatinib tend to be dose related, doses higher than 400 mg should be avoided if possible to decrease the risk and severity of nausea and vomiting. With sunitinib, symptoms that are persistent can be alleviated by switching to the 37.5-mg continuous daily regimen (rather than the 50 mg/day for 4 weeks and then 2 weeks off drug) or reducing the dose.[1]

Diarrhea

Up to 45% of patients on imatinib and 42.5% on sunitinib experience diarrhea that is generally mild and is dose-related. An irregular pattern may be seen in many patients, characterized by normal bowel movements and frequent bowel movements on different days.[1]

Management. As long as the side effect is mild, it may be managed effectively through dietary changes, including consumption of bland foods. If severe, oral hydration and antidiarrheal medications such as loperamide can be used, possibly daily if symptoms persist regularly. Probiotics are often recommended despite the absence of a systematic study evaluating their use.[1]

Hypertension

Sunitinib is associated with hypertension in approximately 28% of patients who receive the drug on a continuous schedule. Imatinib, on the other hand, is not associated with elevations in blood pressure.[1]

Management. Management strategies include:

- Measuring baseline BP before initiation of sunitinib treatment and at least weekly during the first two cycles and once per cycle during subsequent cycles.
- The goal is to keep BP <150/90 mm Hg.[1]
- VEGF inhibitor-associated hypertension can be controlled with angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin II receptor antagonists instead of diuretics.[16] However, caution should be exercise with the use of some calcium channel blockers (diltiazem and verapamil) because of their inhibition of cytochrome P450 isoenzyme 3A4 and interaction with many other medications including sunitinib. Concomitant use of sunitinib with beta-blockers and calcium channel blockers is discouraged because of potential PR interval prolongation. Sunitinib should be discontinued if severe hypertension (>200 mm Hg systolic or >110 mm Hg diastolic) develops.

"Because TKIs are often administered for prolonged periods of time, a crucial factor is the proper management of side effects. For example, discontinuation of imatinib administration results in a rapid tumor progression in the majority of patients with advanced GIST and low imatinib plasma concentrations (<1100 ng/mL) are associated with a short time to disease progression.2 The issue of patient compliance is also a prime concern in assessing the effectiveness of TKIs."

Edema

Periorbital edema (in 47.6% of patients) leg edema (20.4% of patients), facial edema (10.2% of patients), and watery eyes are all common with imatinib. Severe fluid retention may be a risk factor for development of pleural effusions and ascites and an increase in creatinine levels.[1]

Management. Guidelines do not suggest specific treatment for periorbital edema; however, when severe, diuretics can be considered. As long as the condition is mild, a period of watchful waiting is appropriate. Spironolactone is beneficial for patients with hypokalemia or ascites. Nutrition counseling about reducing salt consumption is advised when a 3-kg increase in weight is observed during a 1 week treatment period.[1]

Musculoskeletal Problems

Approximately 40% of patients are affected by musculoskeletal side effects related to imatinib administration.[9] Mild to moderate symptoms typically occur in the hands, feet, calves, and thighs. The legs appear to be the most affected by pain, often predisposed by cold temperatures and exercise. An imatinib dose of 400 mg has been found to be associated with bone pain and arthralgias in up to 14% of GIST patients. Hypophosphatemia and hyperphosphaturia, along with changes in bone and mineral metabolism have also been observed in a large portion of patients on imatinib.

Management. Suggested strategies to alleviate symptoms are:

- Increase daily fluid intake and encourage calcium and magnesium supplements. Monitor blood levels of calcium and magnesium when supplements are taken.
- Anecdotally, the use of warm socks has been reported to reduce the frequency of imatinib-associated muscle cramps.
- In patients with no history of GI bleeding, nonsteroidal anti-inflammatory drugs alleviate bone pain; in patients with a GI bleeding history, misoprostol coupled with a proton pump inhibitor or H2 histamine receptor blocker may be considered.[1]
- Hypophosphatemia with imatinib is probably not clinically significant, requires no treatment, and is usually resolves after cessation of treatment.

Fatigue

Typically, fatigue affects up to 74% of patients on imatinib and up to 65.2% of those on sunitinib.[8,9,11]

Management. The National Comprehensive Cancer Network has published guidelines for cancer-related fatigue and there are steps for managing fatigue associated with TKI therapy. An increase in physical activity has consistently been shown to decrease cancer-related fatigue. If severe anemia is associated with fatigue, blood transfusion or the use of erythropoietin (for blood hemoglobin <10 g/dL) can be considered. Black box warnings for the use of erythropoietin in patients with cancer should be carefully considered and discussed with the patient prior to the use of this drug.[17]

Predicting Toxicities With Imatinib Treatment

One of the areas still not adequately explored is whether predictive models could be developed for determining risk factors for toxicity with TKI treatment. A predictive model has been an elusive goal but one study suggests how these factors can be identified. Van Glabbeke et al[2] identified these factors based on a randomized study of different doses of imatinib:

- Anemia was correlated with dose and baseline hemoglobin level.

- The risk of non-hematological toxicities was dose dependent and higher in females (edema, nausea, diarrhea) and in patients of advanced age (edema, rash and fatigue), poor performance status (fatigue and nausea), prior chemotherapy (fatigue), tumor of identified gastrointestinal origin (diarrhea) and small lesions (rash).

The authors propose a model for calculating risk based on factors identified in their analysis (**Table**). They suggest an interactive risk calculator and propose that this relatively simple tool can be used in clinical practice to customize treatment for individual patients.

References

1. Joensuu H, Trent JC, Reichardt P. Practical management of tyrosine kinase inhibitor-associated side effects in GIST. *Cancer Treatment Reviews.* 2011;37:75-88.
2. Van Glabbeke M, Verweij J, Casali PG, et al. Predicting toxicities for patients with advanced gastrointestinal stromal tumours treated with imatinib: a study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC-ISG-AGITG). *Eur J Cancer.* 2006 Sep;42(14):2277-85.
3. Demetri GD, Wang Y, Wehrle E, et al. Imatinib plasma levels are correlated with clinical benefitin patients with unresectable/metastatic gastrointestinal stromal tumors. *J Clin Oncol.* 2009;27:3141-3147.
4. Demetri GD, van OosteromAT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumor after failure of imatinib: a randomized controlled trial. *Lancet* 2006;368:1329-1338.
5. George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. *Eur J Cancer.* 2009;45:1959-1968.
6. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet.* 2007;370:2011-2019.
7. Desai J, Percori-Giraldi F, McArthur G, et al. Sunitinib malate in the treatment of renal cell carcinoma and gastrointestinal stromal tumor: recommendations for patient management. *Asian Pac J Clin Oncol.* 2007;3:167-176.
8. Verwij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial. *Lancet.* 2004;364:1127-1134.
9. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Eng J Med.* 2002;347:472-480.
10. Gleevec Summary of Product Characteristics 2010;2010.
11. Sutent Summary of Product Characteristics 2010;2010.
12. Botchkareva NV, Khigartian M, Longley BJ, et al. SCF/c-kit signaling is required for cyclic regeneration of the hair pigmentation unit. *FASEB J.* 2001;15:645-658.
13. Luo D, Chen H, Searles G, et al. Coordinated mRNA expression of c-KIT with tyrosinase and TRP-1 in melanin pigmentation of normal and malignant humanmelanocytes and transient activation of tyrosinase by Kit/SCF-R. *Melanoma Res*.1995;5:303-309.
14. Deninger MW, O'Brien SG, Ford JM, et al. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol*. 2003; 21:1637-1647.
15. Griffin JM, Armand MS, Demetri GD. Nursing implications of imatinib as molecularly targeted therapy for gastrointestinal stromal tumors. *Clin J Oncol Nurs*. 2005;9:161-169.
16. Eskens FA, Verweij J. The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) taergeting angiogenesis inhibitors: a review. *Eur J Cancer.* 2006; 42:3127-3139.
17. Juneja V, Keegan, P, Gootenberg, J E, et al. (2008). Continuing reassessment of the risks of erythropoiesis-stimulating agents in patients with cancer. *Clinical Cancer Res*. 2008 14: 3242-3247. ■

Special Considerations to Minimize the Impact of Side Effects

This interview was conducted with Loretta (Lori) Williams, MSN, PhD, Assistant Pro-fessor, Symptom Research CAO, at the University of Texas MD Anderson Cancer Center, Houston, Texas. She has extensively studied the measurement of symptoms, the use of qualitative research methods in the development of patient-reported outcomes measures, the biological mechanisms of symptom production, the effects of genetics on symptoms, and the effects of symptoms on family caregivers of cancer patients.

Q. What are the most emergent management issues when you see adverse effects associated with TKI treatment?

Dr Williams: I would say that the most emergent management issues are the relatively rare adverse effects that can be life threatening such as cardiac effects. From a patient perspective, the really unpleasant but more common side effects that interfere with normal activities and cause significant discomfort or change in appearance, such as – fatigue, muscle cramps, diarrhea, nausea, and swelling, especially in the face, are pretty important. When you know you will be on a drug for a long time, even side effects that may seem mild can become a big deal. Some of these side effects may be able to be managed, but others, such as fatigue, are often hard to do anything about.

Q. Do you see any significant differences with imatinib vs sunitinib and what are the most important concerns?

Dr Williams: There are many side effects that both therapies can cause, such as fatigue, diarrhea, and nausea. Sunitinib tends to cause more skin, indigestion, and sore mouth problems. Many, but not all, of my patients report more severe side effects with sunitinib.

Q. How do you handle the situation in which imatinib is discontinued for adverse effects but in view of GIST progression, the patient should be rechallenged with the drug? Anecdotally, what generally happens in this situation?

Dr Williams: In general if this happens, the patient often will be started back on the imatinib but maybe at a lower dose. If the patient is doing okay on the imatinib at the lower dose, the physician may then try to increase the dose, maybe a little at a time. If the patient starts to have severe problems, then the imatinib may be stopped until the side effect gets better and then restarted at the dose the patient was tolerating. I have seen a few patients get back up to full dose with this stepwise approach.

Q. Have you had good results with imatinib interruption? For how long?

Dr Williams: The safety of interrupting imatinib depends a lot on the disease of the individual patient. This is a decision that is best left to each patient's doctor who knows best that patient's disease characteristics. There are reasons why imatinib may need to be stopped, such as a serious side effect, but it is best to resume imatinib as soon the doctor thinks it is safe.

Q. Has regorafenib made a difference in switching medications after side effects become problematic?

Dr Williams: It is great to have new effective drugs like regorafenib approved for GIST to give more treatment options, both when the disease becomes resistant to another drug and when another drug is poorly tolerated. For reasons we do not completely understand, some patients tolerate one drug better than another. But all drugs used to treat GIST have side effects, some of them very similar.

Q. With imatinib, how viable is dose reduction and in what contexts does it seem to be most effective?

Dr Williams: Giving less than the recommended dose is always a little worrisome, but if a patient simply cannot tolerate an effective drug at full dose, it is worth a try to see if the patient can tolerate a lower dose with the drug still being effective. One possible reason that a patient may not tolerate a drug is because the patient does not metabolize the drug (break down the drug and eliminate it) as quickly as most people. That patient may have more severe side effects because he or she may have more of the drug in his or her body. But that may also mean that more of the drug is getting to the tumor cells. So giving that patient a lower dose may mean that the tumor is being exposed to as much drug as a patient taking a higher dose, and so the lower dose will be just as effective for that patient. There is no guarantee that will happen, but if there isn't another option, the physician and patient may decide it is worth a try. ■

Science For A Better Life

Bayer Oncology is committed to working with patients, caregivers, scientists, and clinicians to bring effective therapeutic options to patients with cancer.

Visit us at www.pharma.bayer.com

Bayer HealthCare

Bayer HealthCare

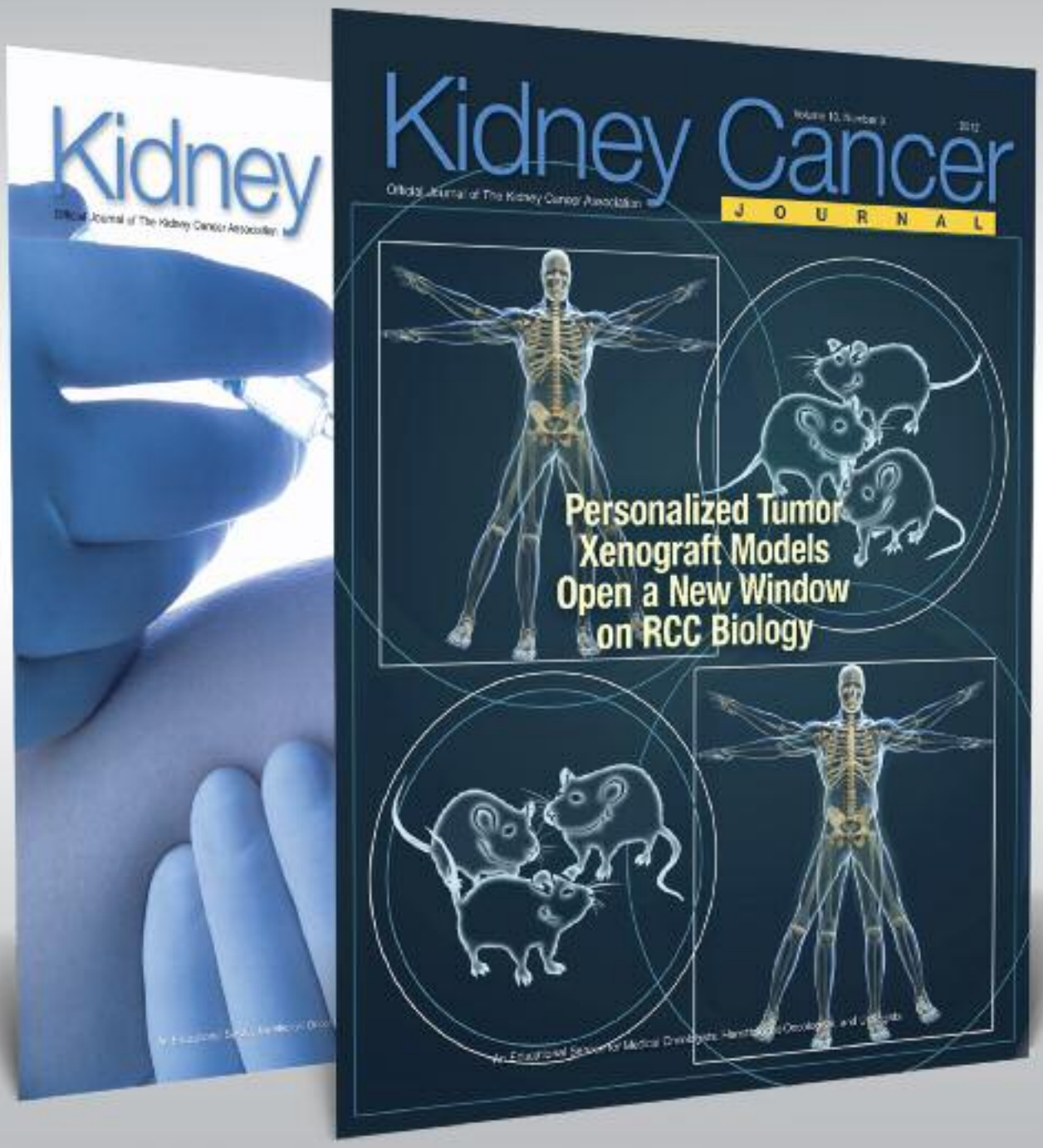
100 Bayer Boulevard, PO Box 915, Whippany, NJ 07981-0915 USA

900-10-0005-14 05/14

NOW IN ITS 12TH YEAR AS AN EDUCATIONAL SERVICE FOR MEDICAL ONCOLOGISTS

The Only Medical Journal Focused Exclusively on Kidney Cancer

- Your comprehensive source of information for renal cell carcinoma
- Peer reviewed
- The official journal of the Kidney Cancer Association



Thank you to our **members, sponsors, physicians,** and **friends** in the GIST community for making 2014 so successful!

Together, we can do anything.

The Life Raft GROUP

www.liferaftgroup.org

GUP Associates
2557 Tulip Street
Sarasota, FL 34239