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
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
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 our 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
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 immune-based approaches. 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
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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. 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 immunobased 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.

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. 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. 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, 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. 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.

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 CD8 T cells to T regulatory cells 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 CD8 T 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 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 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 al15 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.24-26 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 delineates29 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 speculate29 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 study30 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.\(^\text{11}\) 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.\(^\text{8}\)

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).\(^\text{32}\) 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**


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. 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 (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 women 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%).

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 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.

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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. These findings are probably attributable, at 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. In conclusion, 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
SUTENT® (sunitinib malate) is indicated for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate.

**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 observed in animal studies. Monitor blood pressure and treat as needed with standard antiarrhythmic 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.

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

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

**PRIMARY ENDPOINT**

HR=0.33; 95% CI 0.23, 0.47; P<0.001

**Estimated TTP probability (%)**

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**27.3 weeks**

**SUTENT**

**6.4 weeks**

**Placebo**

**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<0.001])
  - 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, 9.3, respectively)

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

- 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®)

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.

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

- 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, 9.3, respectively)

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**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 urinary 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 (35% vs 29%), skin discoloration (20% 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%).
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 anywhere and, in the case of pulmonary tumors, may present as 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 receiving SUTENT. Treatment-emergent Grade 3 or 4 tumor-related hemorrhage was reported 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 21. In two cases, a patient died of 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 haemorrhage. Close monitoring 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 abdominal malignancies treated with SUTENT.

Ulcerative Dyspepsia of the Jaw (OND). ONJ has been observed rarely in patients 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 occurrence 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 accordingly.

QT Interval Prolongation and Torsade de Pointes. QT prolongation and torsade de pointes have been reported in patients with cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

Dyslexia. 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 discontinue therapy and be monitored for signs of thyroid dysfunction performed and be treated as per standard medical practice.

- Treatment-emergent acquired hyperthyroidism 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.

- Heparin therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is no evidence regarding the timing of reintroduction of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy in patients who undergo 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 reduction for 24-hour urine protein of ≥3 g. Discontinue SUTENT for 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 (e.g., 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 EM (adenovirus and secondary to fistula formation). Discontinue SUTENT in patients who develop necrotizing fasciitis.

- Adrenal Function. Physicians prescribing SUTENT are advised to monitor adrenal function in patients who experience symptoms suggestive of hypo- or hyper-thyroidism.

- Adrenal insufficiency was noted in clinical, non-continuous 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 in the adrenal gland were characterized by cell necro-hemorrhage, necrosis, congestion, and hyperplasia and infarction. In clinical studies, C/T/MRI obtained in 326 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in patients treated with SUTENT for renal cell carcinoma (RCC) or a placebo-controlled trial (n=202) for the treatment of GIST. 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 mg/dL (normal >18 mg/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 alkaline phosphatase should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

- Adverse Drug 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=315) 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 dose of 50 mg daily on Schedule 4/2 (4/2).

Grade 3 or 4 treatment-emergent adverse reactions were reported in 56% versus 51% of patients in GIST Study A and Study B, respectively. Grade 1 or 2 treatment-emergent adverse reactions were reported in 97% versus 96% of patients in GIST Study A and Study B, respectively. The most common treatment-emergent adverse reactions occurring in GIST Study A are described below.

- Metastatic cancer progresses at a rapid rate. Treatment with SUTENT has the potential to provide survival benefits to some patients with metastatic cancer. Patients and their caregivers should be advised to consult their healthcare provider if they experience any unexpected adverse reactions, as these may be an indication of disease progression. Patients should be instructed to discontinue treatment with SUTENT if an adverse reaction is considered severe or if it results in unacceptable toxicity or if it is judged unlikely to be reversible.

- Adverse drug 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.

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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 placebo.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SUTENT (n=202)</th>
<th>Placebo (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3/4**</td>
<td>Grade 3/4**</td>
</tr>
<tr>
<td>Any</td>
<td>68 (34)</td>
<td>22 (22)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST / ALT</td>
<td>28 (14)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Lipase</td>
<td>50 (25)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>48 (24)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Amylase</td>
<td>35 (17)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>32 (16)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>20 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased LVEF</td>
<td>22 (11)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Renal/Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>25 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>24 (12)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>20 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>107 (53)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>76 (38)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Platelets</td>
<td>76 (38)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>52 (26)</td>
<td>6 (6)</td>
</tr>
<tr>
<td><strong>LVEF—Left ventricular ejection fraction</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *Note: *Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

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%).

An additional analysis of the study was undertaken to determine the influence of drug-drug interactions on sunitinib disposition. In vitro and in vivo studies indicated that sunitinib does not induce or inhibit major CYP enzymes.

**In Vitro Studies of CYP Inhibition and Induction.** In in vitro studies indicated that sunitinib does not induce or inhibit major CYP enzymes. In the in vitro studies in human liver microsomes and hepatocytes, CYP3A4, CYP2C19, CYP2C28, CYP2C7, CYP2C9, and CYP3A4/48 was not induced in vitro at a dose of 50 μM (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] on the RDD).

**In Vivo Studies of CYP Inhibition and Induction.** In vivo studies were conducted in rats and rabbits following oral administration of sunitinib. In rats, 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). Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at doses of 0.5 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD) and 1 mg/kg/day (approximately 4.7 times the AUC in patients administered the RDD). Significant increases in the incidence of skeletal malformations were observed in rabbits at doses of 0.5 mg/kg/day to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). A high dose of 3 mg/kg/day in rabbits increased the incidence of skeletal abnormalities.

Rats and rabbits were used in these studies because rats and rabbits are species of proven sensitivity to sunitinib. In both species, sunitinib was administered for 13 days. In both species, offspring were observed for 7 days after administration of sunitinib. Offspring observed for 7 days after administration of sunitinib were euthanized at the end of the 7-day observation period.

**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, 1.0, 2.0, 5.0 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at doses 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). Significant increases in the incidence of skeletal malformations were observed in rabbits at doses of 0.5 mg/kg/day to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). A high dose of 3 mg/kg/day in rabbits increased the incidence of skeletal abnormalities.

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**Nursing Mothers.** Sunitinib and its metabolites are excreted in 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 sunitinib, 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. Physiologic plasmin was observed in cynomolgus monkeys with open growth plates treated for 2 or 3 months (3 months dosing 2, 6, 12 mg/kg/day, 4 cycles dosing 3.3, 6, 12 mg/kg/day) with sunitinib at doses that were >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/day) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day) with sunitinib for 3 cycles (15 mg/kg/day), placentofetal carinal uptake and accumulation of sunitinib at doses ≥5 mg/kg/day (approximately 10 times the RDD based on AUC).
physisal 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 2 cycles. In rats the no effect level in bones was <2 mg/kg/day.

Geriatric Use. Of 625 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. Sunitinib 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 overdose 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/m2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypov/vole, 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 gastric duodenal 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-month 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 highest dose level (10 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 mutagen [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 (≥2.4 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 ≥8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3-month study at 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 embryotoxicity 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 56 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 ≥2.5 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
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.

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.
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 vatalanib.

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

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 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.
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. 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.

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. 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.

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.

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.

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
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

### Table. Examples of results for individual patients

<table>
<thead>
<tr>
<th>Patients' characteristics</th>
<th>Dose (mg/d)</th>
<th>Probability of grade 2 (or higher) toxicity (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Oedema</td>
<td>Fatigue</td>
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<tr>
<td>Age (years)</td>
<td>Sex</td>
<td>PS (WHO)</td>
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### Table. Hematological toxicities

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<tr>
<th>HGB (mmol/l)</th>
<th>ANC (10**9/1)</th>
<th>Dose (mg/d)</th>
<th>Probability of grade 3 (or 4) toxicity (%)</th>
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<tr>
<td></td>
<td>HGB</td>
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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
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.\textsuperscript{1} \textbf{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 anti-diarrheal 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.\textsuperscript{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.\textsuperscript{1} \textbf{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.\textsuperscript{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.\textsuperscript{16} However, caution should be exercised 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.

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.\textsuperscript{1} \textbf{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.\textsuperscript{1}

Musculoskeletal Problems
Approximately 40% of patients are affected by musculoskeletal side effects related to imatinib administration.\textsuperscript{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. \textbf{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.\textsuperscript{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.\textsuperscript{8,9,11} \textbf{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.\textsuperscript{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\textsuperscript{16} 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
This interview was conducted with Loretta (Lori) Williams, MSN, PhD, Assistant Professor, 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.
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