Editorial

What drives the wheel towards long-term outcome in advanced GIST, its size, genotype or may be a pill or two of imatinib?

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It is a rare event in the field of oncology therapeutics when a molecule with a selective and narrow spectrum of anti-cancer activity transforms the treatment landscape and outcomes in a previously 'tough to treat' disease. The initial case report, published in April 2001, documenting the remarkable response of a heavily pretreated metastatic patient with GIST to imatinib was one such event that marked a turning point in the biological, diagnostic, and therapeutic approaches to advanced GIST (1). It shows remarkable foresight on the part of the investigators of the EORTC-STBSG/AIGTG and the SWOG groups to start the parallel running large scale trials examining two different dose levels of imatinib (400 and 800 mg) with the advent of the use of imatinib in advanced GIST (2,3). The reasons for the continued relevance of these two studies is multifold: primarily, because of imatinib being active against GIST across varying doses with no clear-cut evidence of superiority of one dose level over another as per initial data. Secondly, the updated results of the EORTC-STBSG/AIGTG study have encompassed almost the entire learning curve of the management of advanced GIST over the last 15 years.

Casali *et al*. have recently published the long-term results of the EORTC-STBSG/AIGTG phase III trial after a median follow-up time of 10.9 years (2). The current update, besides providing a historical perspective and commenting on outcomes of patients treated in an earlier era, has important learning points. The median OS of patients treated with both dose levels was 3.9 years, while the median PFS was 1.7 (400 mg dose level) and 2 years (800 mg dose level), respectively. While the PFS is similar to the updated SWOG data (19 months), more recently published data, albeit with smaller numbers, from other groups have documented increased PFS with first line imatinib, ranging from 34–43 months (4-6). Within the confines of smaller numbers and non-prospective data collection, these differences can be explained by upfront treatment with imatinib in the current era (as opposed to the prior use of ineffective chemotherapy and radiotherapy in the EORTC-STBSG/AIGTG study) as well as reducing tumor size at diagnosis across time-periods. This has been rightfully acknowledged by the authors in their study. While OS can also be affected by the above-mentioned factors, there is also a case for effective second line agents like Sunitinib, Pazopanib and Regorafenib that are currently used and contribute to prolonging survival (7-9). Effective salvage regimens, coupled with selective use of surgery, means that current survivals average up to 6.4 years in certain studies, which is superior to the 3.9 years seen in the EORTC-STBSG/AIGTG study. The authors have commented on the crossover of patients from the 400 mg dose arm to the 800 mg dose arm, but information on non-imatinib salvage therapy is not given. However, information can be gleaned from the also recently published long-term results of SWOG Intergroup Trial S0033, regarding the use of salvage TKIs. In this study, in 142 patients designated

as long-term survivors (≥8 years from enrollment), 54 patients (38%) received additional agents like sorafenib and sunitinib. Whether the use of salvage therapies alone contributed to longer median OS in this study as opposed to the EORTC-STBSG/AIGTG study (5.2 *vs.* 3.9 years) remains a moot point (3).

The authors have made important observations regarding the use of 800 mg dose of imatinib post progression on 400 mg imatinib dosing. While nearly all patients who crossed-over to 800 mg had progressed and the median time on increased dose of imatinib was 3.6 months, interestingly, 17.4% of patients in this cohort had remained on imatinib 800 mg for 1 year. Such data holds promise for patients who may not be able to afford sunitinib or regorafenib. Whether there was a greater proportion of patients with exon 9 mutations who benefitted from this raised dose post progression on 400 mg doses is not answered in the current study.

The long-term outcomes in the study reinforce the benefit of 800 mg doses in exon 9 c-kit mutants in terms of response rates and survival. Multiple studies over the years have confirmed these findings with many guidelines recommending the 800 mg dose level for patients with exon 9 mutations (10-12). While regulatory barriers (as correctly pointed out by the authors) may inhibit the routine use of 800 mg doses in exon 9 mutant GIST, large scale trials with long-term results such as this should help in overcoming such logistic barriers. From a biological and treatment standpoint, it is imperative to maximize outcomes with appropriate dosing of imatinib in patients with exon 9 mutants. This is primarily important because of the degree of benefit offered by salvage drugs post progression on imatinib. The benefit with sunitinib (27.3 *vs.* 6.4 weeks), regorafenib (4.8 *vs.* 0.9 months), while statistically and potentially clinically significant, does not compare with the PFS on first line therapy with imatinib, irrespective of mutation status (7,8). While there is evidence for a preferential benefit of sunitinib in exon 9 mutants, the PFS benefit with first-line imatinib should be maximized and this has been brought out well in the current study (13). It would have been extremely informative if secondary mutation status on repeat biopsies would have been available in patients progressing on imatinib, but this was not feasible when the study was planned. Emerging data from this field also suggests a role for liquid biopsies in identifying secondary mutations of kinase genotypes as opposed to a repeat tissue biopsy (14,15).

Patients with advanced GIST with exon 11 mutations in the imatinib era have superior outcomes compared to other mutant subtypes, be it in the resectable or advanced setting of disease. However, ongoing research has clearly identified that exon 11 mutants themselves are a heterogenous cohort, with varying response rates and outcomes with imatinib. Such a break-up of the exon 11 mutants is not available in this study. The authors of the long-term results of the SWOG study did evaluate the prognostic effect of deletions, insertion/duplications and point mutations as sub-cohorts of the exon 11 mutant population, but there were no significant differences between these groups. What was not addressed was the specific role of the del 557-558 codons in the c-KIT exon 11 mutant, which has repeatedly shown a different biological behavior when compared to other exon 11 mutants (16,17). Future trials, in the adjuvant and advanced setting, need to address dose levels and duration of therapy with imatinib as well as salvage drugs keeping in mind kinase genotypes and their biological behaviour.

The authors have made a striking attempt to look at prognostic factors in long-term survivors, considering 59 patients remained progression free and alive for >10 years, and 120 patients remained alive after 10 years. While the authors did identify certain factors on multivariate analysis that predicted for long-term survivorship, they clearly conclude that beyond tumor genotype, all other factors could be results of statistical play. A majority of the tumor burden related factors (such as ECOG PS at presentation, tumor size, prior chemotherapy, etc.) also may have lesser relevance in current practice as well trials, considering the early diagnosis of GIST nowadays, the routine use of adjuvant imatinib in high risk GIST as well as reducing tumor size at diagnosis in patients with newly diagnosed GIST. The additional use of neoadjuvant imatinib in patients who are initially presenting with unresectable disease may further reduce the relevance of tumor size as a predictor of outcomes (5,18). Answers to long-term survivorship in GIST, as in other tumors, are likely to be identified by assays using next generation sequencing on large scale, rather than purely clinical factors.

The updated results of the EORTC-STBSG/AIGTG study are an important addition to the growing literature on the biology, behavior and long-term survivorship of patients with advanced GIST treated with imatinib. It is based on the experience of researchers who have managed the disease over a period of one and a half decades and chronicles the improvements made in treating GIST

over the same period. The emphasis on clinical factors in estimating prognosis of advanced GIST was markedly more relevant at the time of the conception of the trial and remains important today as well, but more efforts and coordination are required in evaluating the biology of advanced GIST to improve outcomes in this rare disease entity.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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