Editorial

Surgical management of adolescent and young adults with gastrointestinal stromal tumors: it is of value?

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Gastrointestinal stromal tumors (GIST) are the most common sarcomas of the gastrointestinal tract and are characterized by constitutive activation of the KIT or PDGFRA receptor tyrosine kinase (1,2). According the Surveillance, Epidemiology and End Results (SEER) database, the incidence of GIST was 0.32 per 100,000 persons in the United States. The median age was 62 years and primary tumors are located mainly in the stomach (58.7%) and small bowel (31.2%). Up-front surgery is still standard therapy for located GIST (except for located GIST tumors of <2 cm diameter in which observation is an option), while imatinib (a c-KIT tyrosine-kinase inhibitor), is currently used in unresectable or metastatic GIST. Despite that 50% of patients respond to Imatinib therapy, the vast majority of patients develop secondary resistance, with a median time of 2 years (3-5). In metastatic GIST without imatinib progression (either generalized or local progression), several studies suggest that surgical rescue would improve overall survival (6-13). Unfortunately, also in this favourable subset of patients, the value of surgical rescue is on debate, because the lack of a control group (patients treated with imatinib therapy with response and not treated with surgical rescue) to adequately contextualize the clinical benefit.

Fero *et al.*, analyzed in this issue, GIST adolescent and young adults (AYA) patients (defined as those under 40 year) from the SEER database from 1998 through 2011. In this retrospective cohort study 392 AYA patients were analysed, for a total of 5,765 GIST patients (6.8%). From this large cohort of AYA patients, 91 patients were diagnosed with metastatic disease and 55 (60%) were operated. Patients who were surgically managed, have a 5-year OS of 71.5% *vs.* 56.7% for patients treated without surgery (P=0.03). Therefore, the study suggests a substantial benefit for surgery in metastatic AYA GIST patients (14).

A prospective randomized clinical trial (NCT00956072) was designed to evaluate the potential benefit of surgical rescue in patients without progressive disease to imatinib. The study unfortunately was prematurely closed, due poor accrual. An alternative way to answer this important question is to analyze retrospective or prospective cohorts of patients with a case-control comparison. The Spanish Group for Research on Sarcoma (GEIS) evaluated 171 patients, non-refractory to imatinib, in two groups. One group (A) was treated only with imatinib (84%) and the other (B) was treated also with surgical rescue (16%). Median survival was 59.9 months in group A compared to 87.6 months in group B (P=0.02) (15). Park *et al.* evaluated also a cohort of 134 patients, treated with imatinib plus surgery (n=42; 31%) and with imatinib alone (n=92; 69%). Overall survival was significantly longer in the surgical group (median OS; NR *vs.* 88.8 months; P=0.001) (16).

To minimize intrinsic bias, propensity score and inverse probability of treatment weighting, can be applied for analysis. However, to adjust potential bias with this methodology, all the variables that potentially can influence progression-free survival or overall survival should be optimally recorded. In the study of Fero *et al.*, unfortunately the most important clinical (albumin levels, disease free-

interval, ECOG performance status, type of location, number of metastatic sites), and biological variables (type of KIT and PDGFR mutations) are missed. In addition, the study lacks all clinical information regarding imatinib efficacy in both groups of patients. Therefore, we could not firmly conclude that in metastatic AYA group of patients, surgical rescue after imatinib therapy would be indicated.

In conclusion the question of the clinical value of surgical rescue in patients with advanced GIST without progressive disease after imatinib therapy (either in AYA and older adult), is still controversial. Only a worldwide large prospective registry with all clinical variables and analyzed, with optimal methods to minimize intrinsic bias, will give a light in the dark.

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Footnote

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

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