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ABSTRACT

Introduction: Sunitinib is a standard second-line treatment in advanced gastrointestinal stromal tumours (GIST). We aimed to search for predictive factors for grade 3 and 4 toxicity, progression-free survival (PFS) and overall survival (OS) in a GIST reference center patient population, outside clinical trials.

Methods: A retrospective analysis was performed of patients treated in two European Comprehensive Cancer Centers between January 2005 and December 2015. Demographic and clinical features, tumour characteristics and biological parameters were investigated. Logistic regression models were used to find factors associated with grade 3 and 4 toxicity. To identify predictive factors for PFS and OS, variables that were statistically significant in univariate analysis were used in the multivariate Cox proportional hazards model.

Results: Ninety-one patients were included in this analysis. Age >60 years (HR 5.0, \( p = .006 \)) and body weight \(<70\) kg (HR 4.7, \( p = .009 \)) were predictive factors for grade 3 and 4 toxicity. When divided into two categories, non-haematological grade 3 and 4 toxicity was predicted by age >60 years (HR 3.8, \( p = .012 \)) and body weight \(<70\) kg (HR 3.3, \( p = .025 \)) whereas haematological toxicity had no significantly associated predictive factors. The median PFS and OS with sunitinib were 8.8 months and 27.5 months, respectively. The use of imatinib less than six months compared to 6–12 months (HR 0.2, \( p = .013 \)) and to >12 months (HR 0.3, \( p = .016 \)) and liver and/or peritoneal metastases (HR 0.1, \( p < .001 \)) were predictive factors for longer PFS. High neutrophil (HR 3.1, \( p = .04 \)) and platelet count (HR 2.4, \( p = .046 \)) predicted a shorter OS. Flexible sunitinib dosing was associated with superior OS (HR 0.21). In advanced GIST patients treated with sunitinib, older and low-weight patients are at risk for grade 3 and 4 toxicity. Clinical (prior imatinib use and metastases), biological (neutrophil and platelet count) and treatment characteristics independently predict PFS and OS.

Conclusion: In advanced GIST patients treated with sunitinib, older and low-weight patients are at risk for grade 3 and 4 toxicity. Clinical (prior imatinib use and metastases), biological (neutrophil and platelet count) and treatment characteristics independently predict PFS and OS.
Methods

Patients

Patient inclusion criteria were: age ≥18 years, histologically confirmed GIST considered irresectable or metastatic, having been treated with the second-line sunitinib. Exclusion criteria were the following: diagnosis of a second active tumour, prior chemotherapy, insufficient data at day 1 and/or during sunitinib treatment.

Design

A retrospective cohort study was conducted using data from medical records of patients treated at two European Comprehensive Cancer centres (Gustave Roussy in Villejuif, France and Radboudumc in Nijmegen, The Netherlands) between January 2005 and December 2015. Data extracted from the medical records were at least: demographic variables tumour characteristics (genotype, primary tumour size, tumour load at day 1 sunitinib (diameter of the single largest lesion), tumour status, site of metastases), surgery of primary tumour at time of diagnosis, duration of prior imatinib use, performance score(PS) and laboratory test results before sunitinib treatment.

Dose and schedule of administration for sunitinib, modifications of the treatment schedule and all grade 3 and 4 toxicities (according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [16]) reported during sunitinib therapy were extracted.

Arterial hypertension (AH) was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or deterioration of pre-existing AH during the first 3 months of sunitinib treatment.

Standard sunitinib dosing schedules were defined as either 50 mg daily on schedule 4/2 or 37.5 mg as a continuous daily dosing schedule. The sunitinib dosing schedule was considered as ‘flexible’ when a modification in the daily dose and/or administration schedule was made, either at the first prescription of sunitinib or at any moment during the treatment. Both dose reduction (for tolerability) and dose increase (for maximal tumour control) were considered as flexible dosing.

PFS was evaluated according to Response Evaluation Criteria in Solid tumours (RECIST) version 1.1 [17]. Patients who had not progressed and/or died during sunitinib treatment by the end date of the study were censored at the date of the last follow-up. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were used to describe baseline characteristics and events during sunitinib treatment. For toxicity, univariate analysis was performed using the chi-square test or Fisher’s exact test in case of an expected count of less than 20%. Significantly associated factors at a 10% level were entered in a multivariate logistic regression model. Univariate analysis for PFS and OS was performed using the Kaplan–Meier method and compared with the log-rank test for all variables. Only significantly associated factors at a 10% level were included in a multivariate Cox proportional hazards model to identify independent predictive factors for PFS and OS. Factors that had missing data of more than 20% or factors with codependence were excluded from the final models. The analyses were conducted using SPSS version 23.0 (IBM Corp. Released 2015. Armonk, NY: IBM Corp.).

Results

Patient and tumour characteristics

A total of 238 advanced GIST patients were treated with the second-line sunitinib in both centres, of which 91 met the inclusion criteria (69 from Gustave Roussy and 22 from Radboudumc). Their clinical and tumour characteristics are summarized in Table 1.

The selection process in shown in Supplementary Figure 1. The median duration of sunitinib use was 9.3 months (overall range of 0.3–84.2 months). Sixteen (17.6%) patients started sunitinib at the standard dose of 50 mg daily in a ‘4 weeks on–2 weeks off’ schedule, 65 (71.4%) patients were prescribed 37.5 mg on a continuous daily dosing and the remaining patients started on an adjusted, lower dosing schedule. In the period that they used sunitinib, 55 patients (60.4%) received a flexible schedule to manage either toxicity or tumour progression. Forty-nine (53.8%) patients discontinued sunitinib after progression, 12 (13.2%) had to stop because of toxicity. At the cut-off point, 14 (15.4%) patients were still using sunitinib.

Toxicity

Grade 3 or 4 toxicity was observed in 51 patients (56.0%). The most frequent adverse events were grade 3 diarrhoea (13.2%), grade 3 neutropenia (12.1%), grade 3 asthenia (9.9%), grade 3 hypertension (9.9%) and grade 3 hand–foot syndrome (8.8%). Other haematological toxicities that occurred were grade 3 anaemia (2.1%), grade 4 anaemia (4.3%), grade 3 lymphopenia (5.5%) and grade 4 lymphopenia (1.1%). There were no sunitinib related deaths.

Predictive factors for grade 3 and 4 toxicity

For all grade 3 and 4 adverse events were tumour load, age, body weight and platelet count significant after univariate analysis. Age >60 years (HR 5.0, p = .006) and body weight ≤70 kg (HR 4.7, p = .009) remained significantly associated in the multivariate model (Table 2). When split into two categories (non-haematological toxicity and haematological toxicity), age, body weight and tumour load were significant for non-haematological toxicity in univariate analysis. After addition to the multivariate model, age >60 years (HR 3.8, p = .012) and body weight ≤70 kg (HR 3.3, p = .025) remained significant predictive factors (Table 2). Regarding haematological toxicity, the following factors were significant in univariate analysis: site of the primary tumour, serum albumin and serum levels of lactate dehydrogenase (LDH). The
remaining factors were not significantly associated with haematological toxicity.

Survival outcomes

At the time of analysis, 77 patients (84.6%) had progressed during sunitinib treatment with a median PFS of 8.8 months (95% confidence interval [CI], 6.8–10.8 months) and 39 patients (42.9%) were still alive with a median OS of 27.5 months (95% CI 20.6–34.5 months).

Predictive factors for PFS

Univariate analysis identified the following factors significantly associated with a longer PFS: primary tumour size <8 cm, duration of prior imatinib use ≤6 months, age ≥60 years, metastatic disease, liver and/or peritoneal metastasis and neutrophil count ≤7.5 × 10⁹/L. In the final multivariate model, prior imatinib use less than six months compared to 6–12 months (HR 0.2, p = .013) and to >12 months (HR 0.3, p = .016) and liver metastasis (HR 0.1, p < .001), peritoneal metastasis (HR 0.2, p = .003) and both liver and peritoneal metastasis (0.2, p < .001) compared to locally advanced disease only remained significant predictive factors for PFS (Supplementary Table 1). PFS curves from the multivariate model are plotted in Figure 1. A trend towards longer PFS for liver metastasis only compared to peritoneal metastasis only or both liver and peritoneal metastasis was seen, but it did not reach significance (data not shown).

Predictive factors for OS

Tumour load >10 cm, performance score ECOG 2 or 3, neutrophil count >7.5 × 10⁹/L, platelet count >400 × 10⁹/L and serum LDH levels >250 U/L were significantly associated with
shorter OS after univariate analysis. Elevated neutrophil count (HR 3.1, \( p = .042 \)) and platelet count (HR 2.4, \( p = .046 \)) kept significance in the multivariate model, predicting shorter OS (Supplementary Table 2). Survival curves from the multivariate model are plotted in Figure 2.

Although not being a variable that could be added to the multivariate model as it was not determined at day 1 or early after start of sunitinib, treatment flexibility was almost significantly associated with increased PFS (\( p = .114 \)) and a significant predictive factor for longer OS (\( p = .021 \)) in univariate analysis (Figure 3).

**Discussion**

This study demonstrates several factors that impact toxicity and survival in GIST patients treated with second-line sunitinib outside a clinical trial.

In this retrospective ‘real life patient’ cohort, patients had comparable toxicity rates to a previous treatment-use trial [13]. Age and weight significantly predict all types of grade 3 and 4 toxicity. Previous studies have already shown that high age is a significant factor for severe toxicity during sunitinib treatment in patients with advanced RCC, GIST and other types of cancer [14,18]. Body weight has not been previously reported as a predictive factor for toxicity, but low body mass index and low body surface area were significantly associated with dose-limiting or severe toxicities in advanced RCC patients treated with sunitinib [14,15]. Body weight is known to influence sunitinib exposure and several studies have shown a correlation between exposure and different types of adverse events, thus on a pharmacokinetic level body weight is an important factor for sunitinib related toxicity [19,20] suggesting that fixed dosing is not desirable in sunitinib prescription.

When divided in non-haematological and haematological grade 3 or 4 toxicity, multivariate analysis showed that age and weight remained significant predictive factors for the first category but for the latter category that none of the associated factors in univariate analysis could predict toxicity.

In this study, the median PFS of 8.8 months is almost equal to a large multicentre worldwide treatment use trial of sunitinib [13]. In contrast, the median OS of 27.5 months is higher than those previously reported in other series [8,11,13] and similar with OS observed in the phase 2 trial testing sunitinib in a continuous dosing schedule [10]. This difference may be related to the long follow-up period of patients in the current study, the availability of third-line treatments or to flexible sunitinib dosing: a small proportion of patients discontinued because of an adverse event.

After multivariate analysis, short duration of prior imatinib use (\( \leq 6 \) months) and metastatic disease remained significant predictive factors for longer PFS with sunitinib treatment. A short period of imatinib use is often due to an intrinsic resistance of the tumour to imatinib, enhancing the chance of tumour responsiveness to sunitinib. KIT-exon mutation plays an important role in response to imatinib and sunitinib, as exon 9 mutated and wild type GISTs are more likely to be intrinsically resistant to imatinib and show a better response...
to sunitinib [21,22]. PFS was shorter for patients using imatinib 6–12 months versus >12 months, but the difference in PFS between these two groups was not statistically significant.

Increased PFS rates for metastatic disease, with a trend of longer PFS in patients with liver metastasis only compared to peritoneal metastasis only and to both liver and peritoneal metastasis, respectively, could be explained by different concentrations of sunitinib in different organs, as was shown for imatinib [23]. Imatinib concentrations were higher in the liver and omentum compared to the stomach, possibly leading to better local tumour control. However, if sunitinib concentrations significantly differ in tissues from different organs remains to be determined.

Elevated neutrophil count and platelet count at day 1 of sunitinib were significant predictive factors for shorter OS.
The cut-off value for the elevated neutrophil count or ‘Polymorphonuclear leucocytosis’ at $7.5 \times 10^9$ was defined based on the study by Patrixidou et al. [6] who found that for the first-line imatinib, this parameter also significantly predicts overall survival. Neutrophilia and thrombocytosis are caused by an inflammatory response to tumoural activity [24,25] which is also seen in metastatic renal cell cancer [26]. For the latter, neutrophilia and thrombocytosis are part of the validated International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model, predicting lower OS when treated with vascular endothelial growth factor (VEGF)-targeted therapy [27] including sunitinib.

Treatment flexibility was not added to the multivariate models, but it appeared to be an important factor for increased PFS and OS. The same association between adjusted sunitinib dosing and PFS and OS was also found by Reichardt et al. [13], but studies prospectively comparing different dosing schedules to the approved schedule of 50 mg daily ‘4 weeks on–2 weeks off’ are still lacking. As age is a predictive factor for severe toxicity, this is a very important treatment strategy, especially in elderly patients. More research is needed to further investigate optimal treatment in this patient population, but these data show that adjusting treatment based on toxicity and/or tumour response can be a good strategy to prolong sunitinib use and increase survival.

In current practice, it can be valuable to measure plasma sunitinib-levels in order to ensure sufficient exposure to the drug or to determine toxic levels [28]. This facilitates optimizing the sunitinib dosing schedule. Unfortunately, plasma sunitinib-levels were not measured routinely in our included patients, thus, could not be taken into account in our analysis.

In the final multivariate models, some variables had to be excluded because of missing data. Despite this exclusion, the reported predictive factors are clearly significant. In contrast with previous research for predictive factors for survival of sunitinib treatment i.e., tumour genotype, primary tumour localization and arterial hypertension were no significant predictive factors for survival in our study [11,21,22,29]. Unfortunately, in 32 patients, the tumour genotype was not known and secondary mutations were rarely determined. There was a trend towards superior PFS and OS in patients with early arterial hypertension, but it did not reach significance (data not shown). This could be due to missing data regarding this variable in 20% of the patients. Furthermore, gastric acid suppression could not be taken into account due to lack of sufficient information in our population on antacid medication use, where it appears to have a significant impact on sunitinib efficacy in renal cell cancer patients [30]. To identify additional discriminative factors, more and sufficient data is necessary for future studies.

In conclusion, this study provides several demographic, tumoural and biological characteristics as predictive factors for PFS, OS and toxicity of the second-line sunitinib in advanced GIST patients. They will help identify patients who will benefit most from sunitinib treatment and who are at risk for severe treatment-related toxicity. Flexible dosing based on toxicity and tumour response can be an important strategy to further prolong sunitinib use and survival rates. In the era of targeted therapies in advanced GIST, optimization of each subsequent line of TKIs could have a real impact on patient’s outcome, as well as with registered drugs as with new promising agents such as Blu-285 [31] or DCC-2618 [32,33].

Disclosure statement
Dr. den Hollander has nothing to disclose. Dr. van der Graaf reports research grants from Novartis, and fees to her institution from Bayer, outside the submitted work. Dr. Desar has nothing to disclose. Dr. Le Cesne reports personal fees from Pharmamar, personal fees from Lilly, personal fees from Pfizer, personal fees from Amgen, outside the submitted work.

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