Adjuvant Imatinib in Patients with GIST Harboring Exon 9 KIT Mutations: Results from a Multi-institutional European Retrospective Study

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ABSTRACT

Purpose: The effect of high-dose imatinib (800 mg/day) on survival in the adjuvant treatment of patients with resected KIT exon 9–mutated gastrointestinal stromal tumors (GIST) is not established. Here, the association of dose and other clinicopathologic variables with survival was evaluated in a large multi-institutional European cohort.

Experimental Design: Data from 185 patients were retrospectively collected in 23 European GIST reference centers. Propensity score matching (PSM) and inverse-probability of treatment weighting (IPTW) were used to account for confounders. Univariate and multivariate unweighted and weighted Cox proportional hazard regression models were estimated for relapse-free survival (RFS), modified-RFS (mRFS) and imatinib failure-free survival (IFFS). Univariate Cox models were estimated for overall survival.

Results: Of the 185 patients, 131 (70.8%) received a starting dose of 400 mg/d and the remaining 54 (29.2%) a dose of 800 mg/d. Baseline characteristics were partially unbalanced, suggesting a potential selection bias. PSM and IPTW analyses showed no advantage of imatinib 800 mg/d. In the weighted multivariate Cox models, high-dose imatinib was not associated with the survival outcomes [RFS: hazard ratio (HR), 1.24; 95% confidence interval (CI), 0.79–1.94; mRFS: HR, 1.69; 95% CI, 0.92–3.10; IFFS: HR, 1.35; 95% CI, 0.79–2.28]. The variables consistently associated with worse survival outcomes were high mitotic index and nongastric tumor location.

Conclusions: In this retrospective series of patients with KIT exon 9–mutated GIST treated with adjuvant imatinib, a daily dose of 800 mg versus 400 mg did not show better results in terms of survival outcomes. Prospective evaluation of the more appropriate adjuvant treatment in this setting is warranted.

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Translational Relevance

KIT exon-9 gastrointestinal stromal tumors (GIST) are a relatively rare subgroup of GIST. In these patients, our results suggest that in the adjuvant setting, in contrast to what is observed in the advanced setting, treatment with imatinib 800 mg/d is not associated with better survival outcomes compared with 400 mg/d. The retrospective nature of our results and the evidence of physicians' selection bias limit their direct applicability. However, our findings strongly warrant a prospective evaluation of the efficacy of imatinib at different doses – or of other tyrosine kinase inhibitors – in this selected population.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common type of sarcoma arising in the digestive tract and are characterized by the common presence of oncogenic mutations in genes encoding the KIT or PDGFRA receptor tyrosine kinases. The most common *KIT* mutations are in exon 11 and they are present in approximately 70% of the cases. Exon 9 mutations are detected in 9% of all GIST and 22% of small bowel GIST (1, 2). For patients with *KIT*-mutated GIST, the tyrosine kinase inhibitor (TKI) imatinib represents an uniquely successful targeted therapy (3), which is used both as the first-line treatment for advanced disease and as adjuvant treatment for patients at intermediate high risk of relapse (4).

At the standard dose of imatinib (400 mg/day), patients with advanced GIST with *KIT* exon 11–mutated GIST have a higher response rate and a significantly longer median survival compared with patients with exon –mutated GIST (5). An analysis of two randomized trials comparing imatinib 400 mg per day and 800 mg per day in advanced GIST demonstrated a significantly longer progression-free survival (PFS) for patients with *KIT* exon 9 tumors treated with 800 mg per day. No difference in PFS was observed in patients with exon 11–mutated GIST treated at the two doses (6). However, an increase in imatinib dose is frequently offered after progressing on standard dose as a second-line therapy (7). For this reason, imatinib 800 mg per day is often proposed as first-line treatment for patients with metastatic GIST with exon 9 mutations, where national and institutional policies allow it.

Three randomized phase III trials explored the role of adjuvant imatinib treatment in different patient cohorts, with different durations of adjuvant treatment and patient populations (8–10). Based on the SSG XVIII trial, imatinib at 400 mg per day is currently approved as an adjuvant treatment, with a duration of 3 years.

The impact of the mutational status on the benefit from the adjuvant treatment, however, has not been fully clarified. Data suggest that exon 9–mutated GIST might not achieve the same benefit compared with exon 11–mutated GIST (11, 12). Despite the absence of prospective data, patients with exon 9 mutations are often offered imatinib at a dose of 800 mg per day extrapolating from the data for the advanced setting (13). This choice, however, is not based on any prospective evidence and it also dependent on local regulatory authorities.

We therefore retrospectively collected and analyzed data on patients with exon 9–mutated GIST treated in selected European reference centers with adjuvant imatinib at either 400 mgper day or 800 mg per day to elucidate the influence on patient outcome of a higher dose of imatinib in the adjuvant treatment setting.

Materials and Methods

Patient selection

Data for this study were identified via retrospective review of electronic patient records in 23 European GIST reference centers. We selected patients that had received curative surgery for *KIT* exon 9–mutated GIST and started adjuvant treatment with imatinib (400 mg/day or 800 mg/day) between January 2002 and July 2020. Clinical and pathologic variables collected included patient age at diagnosis and gender; tumor localization, largest dimension, and mitotic index; presence or absence of tumor rupture during surgery. We also collected data on the duration of adjuvant treatment, on dose reductions, on the sites of relapse, and on subsequent treatments. Preoperative neoadjuvant imatinib and complete resection of metastatic disease represented exclusion criteria. The study was conducted in accordance with the principles stated in the Declaration of Helsinki and it was approved by the ethics committees of each participating center as per the institutional statutes. Due to its retrospective nature, formal patient consent was not required.

Outcomes

We defined four clinically relevant endpoints: relapse-free survival (RFS), defined as the interval from curative surgery to the date of radiologically confirmed disease relapse or death, whichever occurred first; modified RFS (mRFS), defined as the interval from the end of adjuvant treatment to the date of radiologically confirmed disease relapse or death, whichever occurred first; imatinib failure-free survival (IFFS), defined as the interval from curative surgery to the date of start of a new systemic treatment other than imatinib, the start of a combination of imatinib with a new systemic treatment, or death resulting from any cause, whichever occurred first; overall survival (OS), defined as the interval from curative surgery to death from any cause.

Patient populations

To analyze the different outcomes, we defined specific patient populations. The intended-dose (ID) population included all the selected patients based on the imatinib dose they were originally prescribed at the start of the adjuvant treatment (analogous to a prospective intention-to-treat population). Four patients who were started on imatinib 400 mg per day and escalated to imatinib 800 mg per day within 30 days from the beginning of the adjuvant treatment were included in the 800 mg per day group. The effective-dose (ED) population excluded from the original ID population 21 patients who required dose reductions (analogous to a per-protocol population). The endpoint mRFS was evaluated in a subset of the original ID population who did not include those patients with relapse while on treatment or with adjuvant treatment still ongoing at the time of database lock. The variable "adjuvant duration" was not included in the univariate and multivariate models for RFS and IFFS since the value was not known at the time of curative surgery, but it was included in the models for mRFS. To investigate the impact of selection and confounding biases, we also analyzed subpopulations derived from propensity score matching analyses and pseudopopulations obtained via inverse probability of treatment weighting analyses.

Statistical analysis

Patient characteristics at baseline were compared using χ^2 and Fisher exact test for categorical variables and t test for continuous variables respectively. In case of violations of the normality assumption, the nonparametric Mann–Whitney–Wilcoxon test was used.

Median time of follow up was estimated using the reverse Kaplan–Meier method (14).

Tumor location was dichotomized in gastric versus nongastric. High mitotic index was defined as a mitotic count with more than 5 mitoses per 50 high-power fields. Survival curves were estimated using the Kaplan–Meier method.

To reduce the effect of confounding, propensity score matching (PSM) was used (15). PSM estimates the effect of a treatment, by accounting for the covariates that predict receiving the treatment. The PSM analyses were conducted using the R package MatchIt (16). Propensity scores were derived from logistic regressions using adjuvant dose as the dependent variable and the baseline variables as covariates. A 1:1 nearest neighbor matching with caliper 0.1 was employed to define the matched populations. Jitter and histogram plot were used to determine the goodness of the matching.

Similar to PSM, in the inverse-probability of treatment weighting (IPTW) method, weights are assigned to patients, creating pseudo-populations where treatment assignment is independent of covariates. The IPTW analyses were conducted using the R package RISCA (17). The estimated probabilities to receive a specific dose were based on a logistic regression model with adjuvant dose as the dependent variable and baseline clinical characteristics as covariates. Weights for each individual in the population were calculated based on the inverse probabilities to receive the original treatment.

To study the effect of risk factors on survival, unweighted and weighted Cox proportional hazard regression models were estimated. HRs along with their 95% confidence intervals (95% CI) were reported. The function cox.zph of the R library survival (18) was used to investigate violations of the proportional hazards assumption for the final Cox models (19).

No missing values were present in the data. A P value of less than or equal to 0.05 was considered statistically significant. P values less than 0.10 were reported to the third decimal place, whereas P values higher than or equal to 0.10 were reported to the second decimal place. Statistical analyses were performed using R version 4.0.3 (20).

Results

Patient characteristics at baseline

In total, 185 patients were selected. Of these, 131 (70.8%) and 54 (29.2%) respectively received adjuvant imatinib at a dose of 400 mg per day and 800 mg per day (**Table 1**). The median (minimum–maximum) largest tumor dimension was 75 mm (11–300 mm) in the 400 mg per day group compared with 100 mm (26–230 mm) in the 800 mg per day group. This difference was highly significant ($P < 0.001$). Considering the cutpoint of 10 cm used to define high-risk features, in the 400 mg per day group 34 of 131 (30.0%) patients had tumor with largest dimension more than 10 cm, compared with 26 of 54 (48.1%) patients in the 800 mg per day group. Also, the percentage of tumors with high mitotic index was 58.8% and 74.1% in the 400 mg per day and 800 mg per day groups, respectively ($P = 0.065$). Finally, in the distribution of tumor primary site at diagnosis, there was a relatively higher percentage of duodenal GIST and GIST from other locations in the 400 mg per day compared with a higher percentage of gastric GIST in the 800 mg per day group ($P = 0.055$). Tumor dimension, site, and mitotic activity all contribute to the definition of the Miettinen risk stratification, published in 2006 (21). Given the long period considered for patient selection, our population also included patients with low-risk GIST (14/185 in total), equally distributed between groups (approximately 7.5%). The 800 mg per day group was enriched for patients at high risk compared with the 400 mg per day group ($P = 0.059$). These differences suggested the presence of potential selection or confounding bias. To reduce the effects of confounding, PSM and IPTW were included in the survival analyses.

Table 1. Patient characteristics at baseline.

	Adjuvant 400 mg/d	Adjuvant 800 mg/d	*P* value
Number of patients	131	54	
Largest tumor dimension in mm (median, min–max)	75, 11–300	100, 26–230	<0.001
Site of diagnosis (*n*, %)			0.055
- Stomach	8 (6.1)	8 (14.8)	
- Duodenum	19 (14.5)	4 (7.4)	
- Small bowel	89 (67.9)	40 (74.1)	
- Other	15 (11.5)	2 (3.7)	
High mitotic index (*n*, %)	73 (58.8)	40 (74.1)	0.065
Age in years (median, min–max)	56, 29–80	57.5, 27–79	0.52
Tumor rupture (*n*, %)	20 (15.3)	10 (18.5)	0.66
Female gender (*n*, %)	69 (52.7)	30 (55.6)	0.75
Risk by Miettinen stratification (*n*, %)			0.059
- Low	10 (7.6%)	4 (7.4%)	
- Intermediate	32 (24.4%)	5 (9.3%)	
- High	89 (67.9%)	45 (83.3%)	

Abbreviations: d, day; min, minimum; max, maximum.

Patient outcomes and characteristics after adjuvant treatment

The median follow up in the whole population was 91.1 months (95% CI, 83.8–98.4). Overall, the median RFS (ID population) was 73.1 months (95% CI, 59.5–99.0 months), the median mRFS was 85.1 months (95% CI, 48.3 months-infinite); the median IFFS and OS were respectively 128.6 months (95% CI, 96.4 months-infinite) and 246.0 months (95% CI, 174.0 months-infinite; **Fig. 1**).

Patient characteristics and outcomes after adjuvant treatment are presented in Supplementary Table S1 and Supplementary Fig. S1, respectively. The percentage of patients requiring a dose reduction was significantly higher in the 800 mg per day group (24.1% vs. 6.1%, $P = 0.001$). One patient (1.9%) in the 800 mg per day group and 3 patients (2.3%) in the 400 mg per day group permanently discontinued imatinib due to severe toxicity or poor tolerance. Between the two dose groups, there were no significant differences in: duration of the adjuvant treatment, total percentage of patients experiencing disease relapse during the follow up, sites of relapse. The number of patients that relapsed while on adjuvant imatinib was 28 (21.3%) for 400 mg per day and 10 (18.5%) for 800 mg per day.

No significant differences were also observed for subsequent treatments, although the percentage of patients who went on to receive sunitinib as a first-line treatment for disease relapse was as expected higher in the 800 mg per day group. In 17 of the 28 patients who relapsed while on 400 mg per day, the dose was increased to 800 mg per day. Tumor response was evaluable in 13 of these 17 patients, and the best response was partial response for 3 patients, stable disease for 9 patients, and progressive disease for 1 patient. Median PFS to imatinib 800 mg per day in these 17 patients was 14.0 months (95% CI, 8.3–19.7 months).

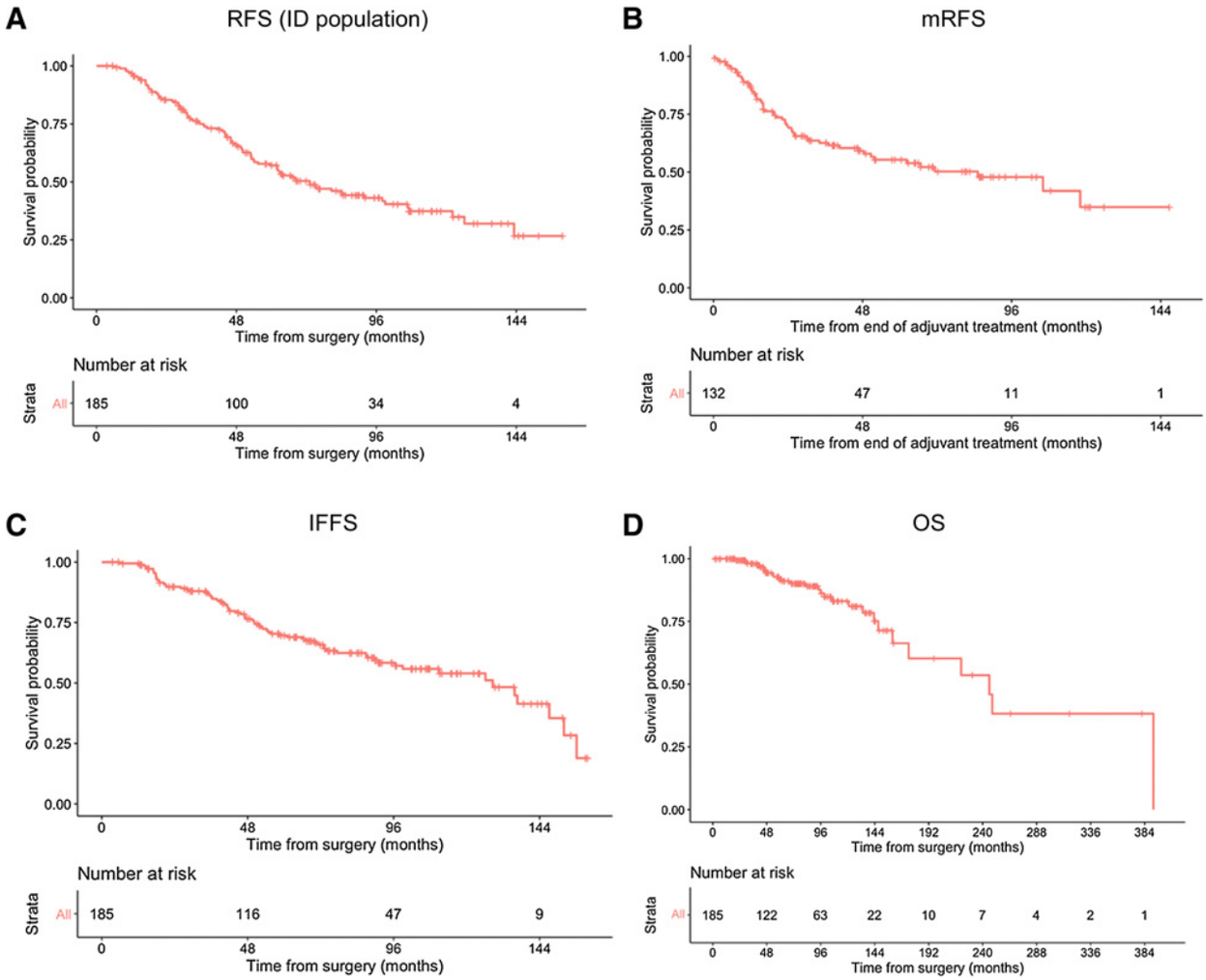

Figure 1.
Kaplan–Meier curves for RFS (**A**), mRFS (**B**), IFFS (**C**), and OS (**D**).

RFS

In the ID population, the median RFS for the 400 mg per day and 800 mg per day group were respectively 80.6 months (95% CI, 62.1–126.2) and 62.0 months (95% CI, 49.8–99.0; **Fig. 2A**).

In the univariate Cox model, mitotic index (HR, 2.67; 95% CI, 1.64–4.34), and tumor primary site (HR, 4.74; 95% CI, 1.50–15.03) were significantly associated to RFS. Imatinib dose (HR, 1.37; 95% CI, 0.89–2.10), gender, tumor dimension, tumor rupture, and age at diagnosis were not associated to survival outcomes (Supplementary Table S2).

PSM and IPTW analyses were used to investigate the role of adjuvant imatinib. The PSM populations comprised 45 patients for

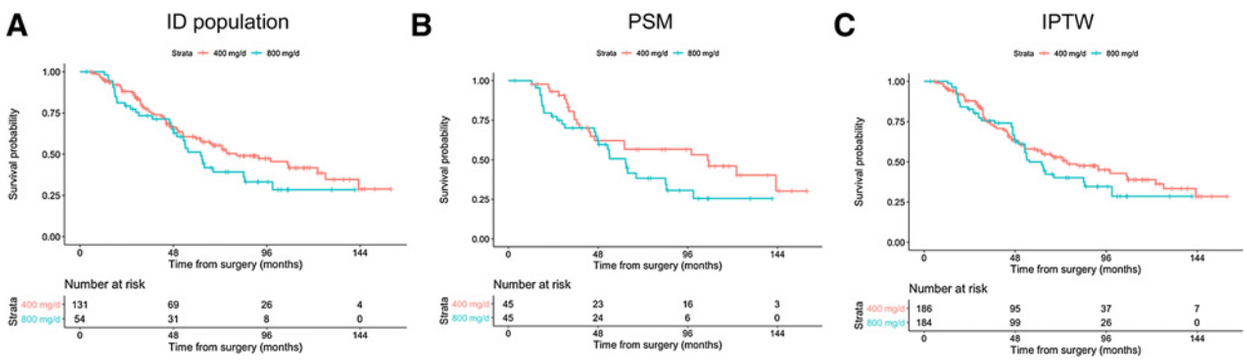

Figure 2.
Kaplan–Meier curves based on adjuvant imatinib dose for RFS in the ID population (**A**), PSM population (**B**), and IPTW pseudo-population (**C**).

Table 2. Multivariate weighted Cox analyses.

	RFS HR (95% CI)	mRFS HR (95% CI)	IFFS HR (95% CI)
Adjuvant dose (800 mg/d)	1.24 (0.79–1.94)	1.69 (0.92–3.10)	1.35 (0.79–2.28)
High mitotic index	2.05 (1.14–3.65)	2.30 (1.05–5.05)	2.09 (1.07–4.09)
Nongastric site	5.83 (1.72–19.74)	8.81 (2.13–36.53)	5.21 (1.13–24.05)
Age at diagnosis (per 10-year increase)	1.17 (0.99–1.39)	1.13 (0.91–1.40)	1.14 (0.95–1.38)
Male gender	1.53 (0.97–2.41)	1.48 (0.82–2.69)	1.52 (0.89–2.59)
Largest tumor dimension (per 10-cm increase)	1.41 (1.00–1.98)	1.47 (0.88–2.45)	1.29 (0.86–1.91)
Tumor rupture	1.64 (0.93–2.88)	1.25 (0.56–2.80)	2.17 (1.23–3.84)
Adjuvant duration (per 1 year increase)	N/A	1.13 (0.85–1.51)	N/A

each group. The jitter and histogram plots suggested good quality matching (Supplementary Fig. S2). The Kaplan–Meier's curve for the PSM populations is shown in **Fig. 2B**. Univariate HR was 1.66 (95% CI, 0.93–2.96). Estimated survival curves based on IPTW analysis are shown in **Fig. 2C**. The weighted univariate HR was 1.22 (95% CI, 0.76–1.93).

Results based the multivariate Cox regression models are shown in Supplementary Table S3 (unweighted) and **Table 2** (weighted). Results in the two models are very similar, with mitotic count and tumor primary site being the variables with the strongest association to RFS.

Univariate and multivariate Cox proportional hazard regression models were also estimated in the ED population, after exclusion of 21 patients requiring dose reductions. The results were similar to those obtained in the ID population (Supplementary Table S2 and Supplementary Table S3).

mRFS

The population for mRFS analysis included 90 patients in the 400 mg per day group and 42 patients in the 800 mg per day group. The median mRFS for the 400 mg per day and 800 mg per day group were respectively 106.1 months (95% CI, 66.7–infinity) and 30.1 months (95% CI, 23.1–infinity; **Fig. 3A**).

In the univariate Cox model, high mitotic index (HR, 3.59; 95% CI, 1.89–6.81), nongastric tumor primary site (HR, 5.48; 95% CI, 1.33–22.54), high-dose imatinib (HR, 1.81; 95% CI, 1.06–3.11) and duration of treatment (HR, 1.30; 95% CI, 1.05–1.59) were associated to mRFS (Supplementary Table S2).

In the PSM analysis, the matched populations comprised of 30 patients each. The jitter and histogram plots suggested a good quality of the matching (Supplementary Fig. S3). The Kaplan–Meier for mRFS curves in the PSM populations are shown in **Fig. 3B**. The univariate HR was equal to 2.36 (95% CI, 1.00–5.59). Finally, in the IPTW analysis, the weighted univariate HR was 1.68 (95% CI, 0.92–3.09; **Fig. 3C**).

In the unweighted (Supplementary Table S3) and weighted multivariate Cox models (**Table 2**), only mitotic index and tumor site retained statistical significance.

IFFS

For the analysis of IFFS, the ID population was used. The median IFFS for the 400 mg per day and 800 mg per day groups were respectively 135.8 months (95% CI, 111.0–infinity) and 91.0 months (95% CI, 67.3–infinity; **Fig. 4A**).

In the univariate Cox analysis, high mitotic index (HR, 2.99; 95% CI, 1.66–5.40), nongastric tumor primary site (HR, 4.61; 95% CI, 1.13–18.83) and older age at diagnosis (HR, 1.24; 95% CI, 1.02–1.51) were significantly associated to IFFS, whereas imatinib dose (HR, 1.47; 95% CI, 0.90–2.41) and all the other variables were not (Supplementary Table S2).

For the PSM analysis, the same matching strategy used for RFS (Supplementary Fig. S2) was applied. The HR in the PSM population was 1.78 (95% CI, 0.93–3.42; **Fig. 4B**). In the IPTW analysis, the HR was 1.30 (95% CI, 0.77–2.20; **Fig. 4C**).

Weighted (**Table 2**) and unweighted (Supplementary Table S3) multivariate Cox models showed a significant association of the outcome with mitotic index and tumor primary site. Tumor rupture was also a significant adverse predictive factor in the weighted model.

OS

For the analysis of OS, the ID population was used. The median OS for the 400 mg per day and 800 mg per day groups were respectively 220.8 months (95% CI, 174.2–infinity) and 248.5 months (95% CI, 106.0–infinity; Supplementary Fig. S4).

Given the low number of events (28 in total, of which 21 in the 400 mg/day group and 7 in the 800 mg/day), only univariate Cox model and IPTW analysis were performed. In the univariate Cox model, the only variable significantly associated to OS was age at

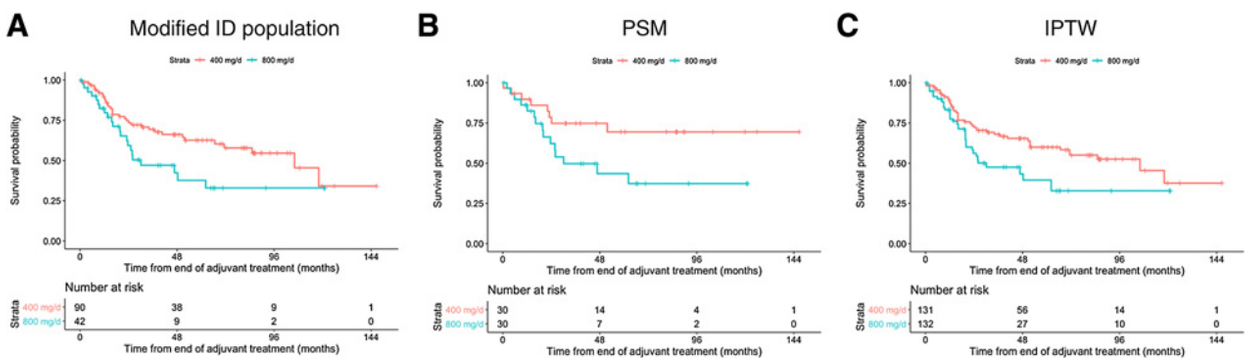

Figure 3.
Kaplan–Meier curves based on adjuvant imatinib dose for mRFS in the modified ID population (**A**), PSM population (**B**), and IPTW pseudo-population (**C**).

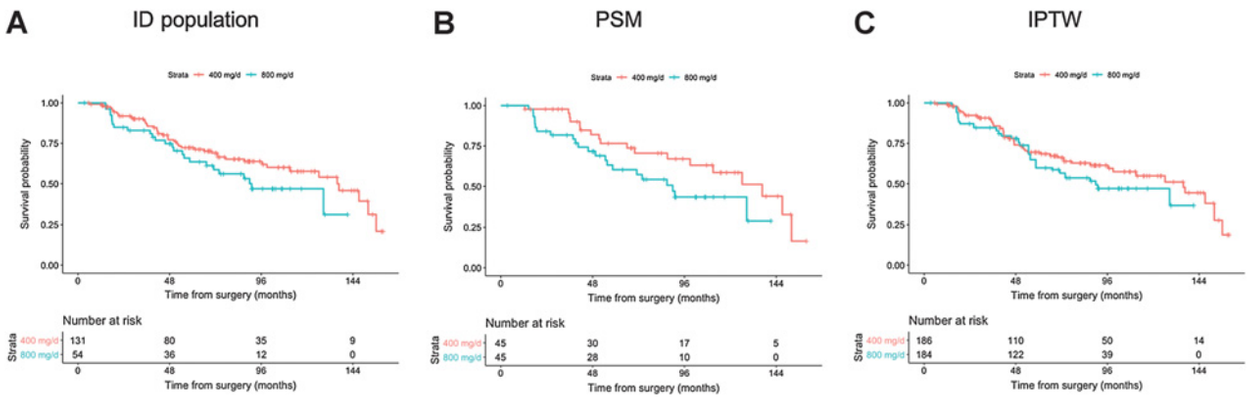

Figure 4.

Kaplan–Meier curves based on adjuvant imatinib dose for IFFS in the ID population (**A**), PSM population (**B**), and IPTW pseudo-population (**C**).

diagnosis (HR, 1.53; 95% CI, 1.12–2.10). The HR for imatinib dose was 1.02 (95% CI, 0.42–2.45). The HRs for the other variables were similar to those observed in the previous analyses. The larger confidence intervals were influenced by the lower number of events (Supplementary Table S2). In the IPTW analysis, the HR for the imatinib dose was 0.81 (95% CI, 0.32–2.07; Supplementary Fig. S4).

Discussion

In this multi-institutional retrospective case series analysis of 185 patients with *KIT* exon 9–mutated GIST who received adjuvant imatinib either at 400 mg per day or 800 mg per day, depending on institutional policies and/or physician's choice, we did not find any statistically significant and/or relevant difference between the two cohorts in terms of RFS, mRFS, IFFS, and OS. Higher mitotic count and nongastric primary tumor site were associated to survival outcomes.

The retrospective nature of this study leads to the presence of confounding factors. In our population, patients with gastric GIST represented 8.6% of the total. This is higher than a reported 4.7% of *KIT* exon 9–mutated GIST of gastric origin with intermediate- or high-risk characteristics (2). This might be because patients who received neoadjuvant imatinib, a population known to be enriched for GIST of nongastric origin, were excluded from our study. Our two cohorts were also unbalanced for the percentage of cases with high mitotic count and median largest tumor dimension, suggesting that treating physicians, when given the choice, were more likely to offer the higher imatinib dose to patients with negative prognostic factors. In itself, the tendency to prescribe a higher imatinib dose to patients at higher risk of relapse might represent a clinician's cognitive bias (22). Notably, our groups also included 7% of patients in each group with a low-risk GIST by Miettinen (21). The presence of these biases is a common feature of real-world studies that limits their value in comparison to randomized clinical trials (23). However, the use of statistical tools such as PSM and IPTW allows to mitigate these biases, at least in part.

Overall, our results are superimposable to available studies. Indeed, in the most recent update of the 3-year adjuvant trial on adjuvant imatinib, the 5-year RFS was 71.4% and 53.0%, respectively, in the 36-month group and in the 12-month group, with the small group of exon 9–mutated GIST showing no significant benefit from a longer treatment (24). In our retrospective analysis, in the whole ID population the median RFS was about 6 years and the estimated 5-year RFS was 57.1% (95% CI, 49.9–65.4%). Moreover, our multivariate analyses confirm the effect on RFS of well known prognostic factors (e.g., high mitotic index, nongastric tumor primary site; ref. 25).

The evidence in favor of high-dose imatinib in patients with *KIT* exon 9–mutated GIST is based on retrospective analyses of trials in the advanced disease setting (26). In fact, the molecular mechanisms underlying the relative resistance of exon 9–mutated GIST to imatinib 400 mg per day are unclear. Exon 11 mutations alter the autoinhibitory properties of KIT juxtamembrane domain and/or compromise the binding of negative regulators that dephosphorylate the KIT kinase domain (27), while exon 9 mutations arise in one of extracellular domains and are believed to enhance the ligand binding affinity and dimerization of KIT monomers (28). Importantly, imatinib only binds to the inactive form of KIT and this binding affects the stability of the autoinhibitory domain of exon 11 (29). Therefore, it can be speculated that in exon 9–mutated GIST the KIT signaling might be more dependent on the presence of the KIT ligand stem-cell factor, which is often expressed by GIST (30), and that imatinib more directly disrupts the conformational changes caused by exon 11 mutations. This is supported by the fact that *in vitro KIT* exon 9–mutated GIST cells were shown to be less addicted to KIT signaling and were able to use alternative signaling mechanisms to drive cellular proliferation (31). Moreover, *KIT* exon 9–mutated GIST had a distinctive transcriptional profile compared with exon 11–mutated GIST. In particular, genes involved in the WNT pathway were upregulated in *KIT* exon 9–mutated GIST (32). The activity of imatinib at 800 mg per day in *KIT* exon 9–mutated GIST in the advanced setting might therefore derive by conditions requiring a macroscopic disease, such as a higher exposure to autocrine stimulation of KIT by stem-cell factor.

The analyses performed in this study suggest that 800 mg per day is not associated to better survival outcomes compared witgh 400 mg per day. If prospectively confirmed, this would be clinically relevant, as high-dose imatinib has a worse toxicity profile. Moreover, considering the relatively poor outcomes of the few patients with *KIT* exon 9–mutated GIST enrolled in available randomized clinical trials (11, 12, 24), the role of adjuvant imatinib in *KIT* exon 9–mutated GIST remains to be clearly defined. In a small series, a benefit from imatinib 400 mg per day in high-risk patients with exon 9–mutated GIST compared with no treatment was recently reported (33). At the current stage, it should be however highlighted that our retrospective real-world evidence is not sufficiently strong to recommend any change to current therapeutic standards and policies.

In conclusion, it would be important to further investigate adjuvant imatinib therapy specifically in patients with *KIT* exon 9–mutated

GIST. The very fact that up to 30% of these patients are treated in expert centers with a dose of 800 mg per day despite the lack of any prospective study underscores how direct evidence would be needed. Our results have been generated by a large collaborative network of more than 20 European centers. Although challenging, this kind of collaborative networks could and should embark on a well designed prospective study to definitively clarify the role of adjuvant imatinib in patients with *KIT* exon 9–mutated GIST. Such a trial would represent the benchmark study in this extremely rare setting, would allow future physicians and policy makers alike to recommend treatments with higher levels of evidence, and would provide the opportunity for longitudinal translational studies to better study the biological behavior of *KIT* exon 9–mutated GIST. Considering the relatively good toxicity profile of imatinib 400 mg per day, we believe that such a study should compare the current standard of imatinib 400 mg per day against either 800 mg per day or novel TKIs, while further observational evidence should be generated about the prognosis of patients with exon 9–mutated GIST who do not receive any adjuvant therapy. Currently, there are no open trials specifically recruiting patients with *KIT* exon 9–mutated in the adjuvant setting and, considering the results of our large multicenter study, an additional effort should be supported on an international basis to clarify the role of adjuvant therapy in this setting.

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Note

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