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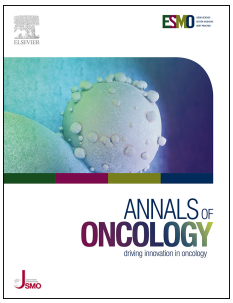
2021-04

Eriksson , M & Joensuu , H 2021 , ' Adjuvant imatinib for GIST : duration likely matters ' , Annals of Oncology , vol. 32 , no. 4 , pp. 434-436 . https://doi.org/10.1016/j.annonc.2021.01.073

http://hdl.handle.net/10138/341622
https://doi.org/10.1016/j.annonc.2021.01.073



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PII: S0923-7534(21)00101-0

DOI: https://doi.org/10.1016/j.annonc.2021.01.073

Reference: ANNONC 469

To appear in: *Annals of Oncology*

Received Date: 22 January 2021

Accepted Date: 23 January 2021

Please cite this article as: Eriksson M, Joensuu H, Adjuvant imatinib for GIST: duration likely matters, *Annals of Oncology* (2021), doi: https://doi.org/10.1016/j.annonc.2021.01.073.

Editorial

Adjuvant imatinib for GIST: duration likely matters

No effective systemic treatment was available for advanced gastrointestinal stromal tumour (GIST) until the introduction of the tyrosine kinase inhibitor (TKI) imatinib in the beginning of the millennium, with a median patient survival time of just 10 to 20 months [1]. Imatinib was first developed for the treatment of chronic myeloid leukaemia, but it also inhibited aberrant gene products of *KIT* and *PDGFRA* that are considered the main drivers of most GISTs. After the treatment of a GIST patient with imatinib 20 years ago leading to a remarkable response [2], multicentre trials confirmed imatinib efficacy in about 85% of patients with advanced GIST [3,4]. Imatinib became the first useful TKI for a solid cancer and a role model for the new era of small molecule targeted cancer drugs.

Many GISTs recur despite macroscopically complete surgery, often with metastases in the peritoneum and/or the liver. With the astonishingly good imatinib efficacy in advanced GIST, it was logical to initiate randomised trials to evaluate adjuvant imatinib. Three such trials have now been performed, each investigating the standard oral daily dose of 400 mg. The first trial was the US American College of Surgeons Oncology Group (ACOSOG) Z9001, a placebo-controlled study evaluating 1 year of adjuvant imatinib after macroscopically complete surgery in patients whose GISTs were ≥ 3 cm in size [5]. The study found adjuvant imatinib to improve recurrence-free survival (RFS), but not overall survival (OS), possibly because patients responded well to imatinib after GIST recurrence.

The 2 later randomised multicentre trials were both open-label studies. The Scandinavian Sarcoma Group (SSG)XVIII/German (AIO) trial compared 3 years to 1 year of adjuvant imatinib, including only patients with a high estimated risk for recurrence according to the modified National Institutes of Health (NIH) criteria [6]. After a median of 10 years of follow-up, the patients treated with 3-year imatinib had longer RFS, and they also survived substantially and statistically significantly longer than patients treated for 1 year (10-year OS 79% vs. 65%, respectively) leading to a hazard ratio (HR) of 0.55 (95% CI, 0.37-0.83) for OS between the groups in the intention-to-treat population. An even lower HR of 0.50 for death was observed in the “true adjuvant population”, when the few patients who did not have GIST in central pathology review and those who had metastases on the date of study entry were excluded [7].

The final results of the third trial, the EORTC/Intergroup trial, are now reported in the *Annals* after a median patient follow-up time of 9.1 years [8]. The trial accrued 908 patients with either an intermediate risk or a high risk for GIST recurrence. The patients were randomly assigned in a 1:1 ratio to receive either adjuvant imatinib for 2 years or to a control group that was observed without systemic treatment. The trial primary endpoint was initially OS, but at the time of the planned interim analysis of the trial [9] it seemed apparent that keeping OS as the primary endpoint would lead to an unreasonably long duration of the trial. The primary endpoint was changed to “imatinib failure-free survival” (IFFS), an estimate of the time to imatinib drug resistance, defined as the time interval from the date of randomization to the date of switching imatinib to another TKI at any time during or following the adjuvant period. The idea was to assess which strategy prolonged the time to

imatinib resistance greater, comparing starting imatinib as adjuvant treatment immediately after surgery or starting it only at the time of GIST recurrence. Adjuvant imatinib improved neither IFFS (HR 0.87, 95.7% CI [0.65; 1.15]) nor OS (HR 0.88, 95% CI [0.65; 1.21]), but it statistically improved RFS significantly (HR 0.71, 95% CI [0.57; 0.89]) compared with the observation group. The RFS improvement seemed mostly temporary, as the 5-year RFS rates favoured the imatinib group (70% vs 63%), but with little difference in the 10-year RFS rates between the groups (62.5% vs 61%).

How do we interpret these findings in the light of the more favourable results from the SSGXVIII/AIO trial, where 3-year adjuvant imatinib reduced deaths as much as 50% compared to 1-year of imatinib, suggesting that adjuvant imatinib can be highly efficacious? The authors write that adjuvant imatinib "may give some OS benefit on the long run …. but the benefit would be limited". One obvious difference between the EORTC/Intergroup trial and the SSGXVIII/AIO trial is the longer duration of imatinib administration in the SSGXVIII/AIO. Two years of adjuvant imatinib may simply be too short to demonstrate the full impact of adjuvant imatinib on OS considering the confounding effect from the substantial efficacy of imatinib on overtly recurrent GIST.

Patient selection for adjuvant imatinib is also likely of great importance, since all GIST patients do not benefit from adjuvant imatinib. GIST may harbour mutations that confers imatinib resistance, such as *PDGFRA* exon 18 mutation D842V [10]. Importantly, over half of the patients in the EORTC/Intergroup trial had an intermediate-risk GIST or rarely even low-risk GIST. The great majority of such patients are now known to be cured by surgery alone [6] and are, therefore, unlikely to benefit from any duration of adjuvant imatinib. Not surprisingly, these patients derived no benefit from the 2-year imatinib treatment. The subset of patients with high-risk GIST in the EORTC/intergroup trial is, on the other hand, of considerable interest. In line with the SSGXVIII/AIO data, there was a non-significant trend in favour of the imatinib arm in IFFS and OS in the high-risk subset of the patients, although the criteria for the high-risk differed somewhat from the criteria used in the SSGXVIII/AIO trial [7].

Early discontinuation of imatinib may also have diluted imatinib efficacy in the EORTC/Intergroup trial. Despite that an imatinib dose of 400 mg/day is usually well tolerated and there was a possibility to reduce the dose for toxicity, 21% of the patients discontinued imatinib for reasons other than recurrence or death, mostly due to toxicity.

What about the suggested new endpoint for adjuvant trials, IFFS? The suggestion to use IFFS-like primary endpoints in adjuvant trials seems an innovative idea, which may be worthy of further evaluation when the adjuvant agent and the first-line agent are the same. In such trials re-starting of the investigational agent at the time of cancer recurrence needs to be guided in detail in the study protocol from the study start, which was not the case in the intergroup trial. The purpose of adjuvant treatment is to increase the cure rate or to prolong OS without decreasing quality-of-life, and merely longer RFS may not always justify adjuvant treatment in the absence of survival prolongation, even though imatinib was approved for adjuvant treatment based on the RFS findings in the ACOSOG Z9001 trial. However, OS is a more robust endpoint than IFFS, and the SSGXVIII/AIO trial data demonstrate that OS can be selected as one of the key endpoints for adjuvant trials to be carried out in high-risk GIST.

In conclusion, the results of the EORTC/Intergroup study are compatible with the results from the SSGXVIII/AIO trial, even though they do not confirm improved OS with adjuvant imatinib. Taken together, the results from the 3 randomized studies suggest that careful patient selection for adjuvant imatinib is of critical importance and that administration of adjuvant imatinib for a long enough duration is likely needed. At present, 3 years of adjuvant imatinib remains the standard of

care for patients who are at a high risk for GIST recurrence, despite macroscopically complete surgery, and who have a GIST mutational status that suggests sensitivity to imatinib. Evaluation of the safety and efficacy of greater than 3-years' duration of adjuvant imatinib remains a high priority, and two such trials are currently accruing patients (NCT02413736 and NCT02260505), comparing 3 vs 5 years' duration and 3 years' duration vs up to 6 years of treatment, respectively.

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Funding

None declared.

Disclosure

Dr Eriksson is a consultant for Blueprint Medicines, and has participated in advisory boards for Clinigen and Bayer. He is trial physician in the Scandinavian Sarcoma Group, which receives trial support from Novartis.

Dr Joensuu has had a co-appointment at Orion Pharma, has received fees from Neutron Therapeutics, and owns stocks of Orion Pharma and Sartar Therapeutics. He is currently the Chair of the Scientific Advisory Board at Orion Pharma and at Neutron Therapeutics Ltd.

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