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Inconclusive but near the Truth: EORTC Adjuvant Therapy Trial for GIST

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Editorial

At the end of 2015, an important study on adjuvant therapy for gastrointestinal stromal tumors (GISTs) was published in the Journal of Clinical Oncology [1]. The study was a randomized controlled trial (RCT) conducted by the European Organisation for Research and Treatment of Cancer (EORTC) in collaboration with other cancer trial groups. Current clinical guidelines of many countries recommend adjuvant therapy with imatinib, a selective tyrosine kinase inhibitor (TKI), following resection of primary GISTs with a significant risk of recurrence [2-4]. However, despite global consensus, the recommendation is not firmly underpinned by solid evidence. There is no clinical study demonstrating the survival benefits of the adjuvant therapy with this TKI in postoperative patients with primary GISTs. "Survival" mentioned herein refers to overall survival (OS), not recurrence-free survival (RFS).

RFS is frequently used as the surrogate endpoint of OS in current clinical trials because the evaluation of OS is a time-consuming task. Although the methodology is generally reasonable, some GIST experts have expressed concern that the general rule does not hold true in the case of GISTs. Imatinib, a TKI used for adjuvant therapy for GISTs, is characterized by high clinical efficacy that is mediated by the inhibition of the pathogenic activation of KIT receptors [5]. The discontinuation of imatinib inevitably leads to early disease relapse; namely, although imatinib controls the disease well for a long time, some tumor cells survive in the dormant state. Owing to the unique nature of imatinib, the ACOSOG Z9001 trial [6], the first RCT addressing adjuvant therapy for primary GISTs, showed equivocal findings that consequently led to failure of building a global consensus on the clinical benefits of imatinib adjuvant therapy (IAT) for GIST patients. In the ACOSOG Z9001trial, 713 patients who underwent macroscopically complete resection of primary GISTs were randomly assigned to the placebo group and the IAT group (one-year treatment), and the survivals of the two groups were compared. RFS, the primary endpoint of that study, was significantly better in the IAT group than in the placebo group, and the hazard ratio (HR) was 0.35 (95% confidence interval, 0.22-0.53). Many patients, however, suffered from recurrence after completion of one-year IAT. The three-year RFS rates of the two groups were very similar. The rapid decrease in RFS after completion of IAT was notable in patients with high-risk GISTs, a subgroup with markedly increased clinical need for adjuvant therapy. These findings suggested that IAT could retard recurrence but offered no change to the long-term outcomes of GIST patients. Thus, the concern that IAT provides no substantial benefit to GIST patient survival remains.

That concern was largely appeased by the next RCT conducted by the Scandinavian Sarcoma Group (SSG) and the German Working Group on Medical Oncology (AIO). In the SSGXVII/AIO trial [7], 397 patients who underwent macroscopically complete resection of high-risk GISTs were recruited and assigned to one- and three-year IAT groups. RFS was also set as the primary endpoint of that trial. RFS of the three-year IAT group was significantly higher than that of the one-year IAT group (HR, 0.46; five-year RFS rate, 65.6% vs. 47.9%, respectively). Furthermore, the three-year IAT group had significantly higher OS than the one-year IAT group (HR, 0.45; five-year OS rate, 92.0% vs. 81.7%, respectively). The results supported the understanding that IAT improves GIST patient survival and led to the current global recommendation that IAT for three years is needed for patients with high-risk GISTs. However, OS was also evaluated as the secondary endpoint in the SSGXVIII/AIO trial. Thus, a number of GIST experts remain skeptical of the survival benefits of IAT.

The EORTC trial [1] was a long-awaited study because it was the first to set OS as the primary endpoint in RCTs for the adjuvant therapy for GISTs. In that trial, patients who underwent macroscopically complete resection of primary GISTs with intermediate or high risk were recruited. The patients were randomly assigned to the two-year IAT group and the no adjuvant therapy group (control group).

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As the task of clarifying whether or not the selective TKI could improve OS of GIST patients was extremely challenging, the study group had to amend the trial procedures in course of the study. First, they changed the planned target sample size from 400 to 900 patients because the number of recruited patients with intermediate-risk GISTs and the estimated survival rate in the control group were much larger than initially expected. Second, they changed the primary endpoint from OS to imatinib-failure-free survival (IFFS). The reported median survival time (MST) of patients with metastatic GISTs who underwent imatinib therapy was 57 months [8], and a significant number of patients now can survive for more than 10 years. It was presumed that the long-standing disease control by salvage imatinib therapy would obfuscate the impact of IAT on patient survival. Thus, as the need for a new surrogate estimate of OS became apparent, IFFS was devised in the trial. IFFS is defined as the time until GIST becomes uncontrollable by imatinib therapy, or simply put, the time to appearance of imatinib secondary resistance. GIST patients suffering from imatinib secondary resistance finally succumb to the disease owing to progression; it is reported that MST after determination of imatinib secondary resistance is 22 months [9]. Thus, IFFS is considered to be a much more reliable estimate of survival in patients undergoing IAT for GISTs than RFS.

Despite those efforts, the EORTC trial failed to provide definitive evidence that IAT improved GIST patient survival after surgery. IFFS, the primary endpoint of that study, showed no significant difference between the two-year IAT group and the control group; the five-year IFFS rates were 87.0% and 84.1%, respectively. In addition, OS was almost equal between the two patient groups (92.7% vs. 91.8% at five years).

Based on the results of the EORTC trial, what adjuvant therapy should we consider for GIST patients? The EORTC trial was a high-quality study; it had an enrollment of more than 900 GIST patients, a long follow-up time with median of 4.7 years, and IFFS as the primary endpoint. This author thinks that despite the lack of conclusive results, the study correctly indicated the direction toward the optimized selection of patients who really need IAT after GIST surgery.

Tumor criterion based subset analysis showed only a few imatinib-failure events in patients with intermediate-risk GISTs (n=380). Excellent IFFS was observed even in the control group, allowing us to conclude that intermediate-risk GISTs should be excluded from the indication for IAT. The subset analysis also revealed a better IFFS trend in the IAT group of patients with high-risk GISTs (n=528, p=0.087). These findings suggested that the negative results on IFFS of overall population were mainly due to the good survival of patients with intermediate-risk GISTs and the potential survival benefit of IAT in high-risk GIST patients. As regards OS, on the contrary, the Kaplan-Meier curves of patients with high-risk GISTs were very similar between the two groups. These findings seemed to contradict the current understanding that IAT is necessary for high-risk GIST patients. The SSGXVIII/AIO trial had more patients with tumor rupture, an extremely high risk factor for recurrence, than the EORTC trial (20% vs. 11%). A similar trend was seen for tumors with high mitotic indices (>10/high power field) (39% vs. 21%). The difference in patient population between the two trials may have resulted in the conflicting OS data. Overall, IAT is indispensable to patients who have a very high risk of recurrence, as indicated in the SSGXVIII/AIO trial, whereas it would be optional for patients who have a moderate risk of recurrence regardless of pathological tumor classification. It should be noted, however, that the no-adjuvant strategy would be a reasonable choice when recurrence is detected early on and salvage imatinib therapy is implemented.

The EORTC trial provided solid information for considering the IAT strategy for GIST patients, although it failed to demonstrate the need for IAT. The new results of the EORTC trial will prompt us to reconsider the recommendation of IAT for GIST patients. The European Society for Medical Oncology revises the clinical guidelines for GISTs every two years. Special attention is given to how European experts will clinically interpret their own study.

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