Duration of endocrine therapy and its impact on the results of adjuvant trials in premenopausal breast cancer patients

Gnant et al. presented the final results of the Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12) trial after a median follow-up of 94.4 months [1]. Although there was no disease free survival (DFS) difference between patients who received ovarian function suppression (OFS) plus either tamoxifen or anastrozole, patients treated with anastrozole + OFS had a significantly worse overall survival (OS) compared with patients treated with tamoxifen + OFS (hazard ratio = 1.63; 95% confidence interval 1.05–1.45; P = 0.030). These results contradict the results of the combined analysis of SOFT/TEXT trials which showed that 5 years of an aromatase inhibitor (AI) + OFS was associated with a superior DFS when compared with 5 years of tamoxifen + OFS and similar OS. Moreover, these results also contradict the results of numerous trials in the postmenopausal setting that have consistently shown a clear superiority of AI over tamoxifen in DFS and in some trials even an OS benefit [2].

This raises a relevant question regarding the design of the Austrian study and the importance of the duration of adjuvant endocrine therapy, which was only 3 years in the ABCSG-12 trial. Although the authors referred to discrepancies in post-relapse therapy as a possible confounding factor to the poorer OS in the anastrozole arm, they did not address whether some patients were offered further adjuvant therapy ‘off study’ beyond the initial 3 years. Unless the study protocol controlled treatment beyond 3 years and in light of its open-label design, it is plausible that many patients in the control arm (tamoxifen + OFS) would have been offered by their treating physician additional tamoxifen to complete the classic 5-year therapy [3]. In contrast, a continuation of adjuvant therapy beyond 3 years would less likely occur in the investigational arm (anastrozole + OFS) where extension of endocrine therapy is not supported by evidence in the premenopausal setting.

This would make it difficult to interpret the hazard rate beyond the initial 3 years of treatment. Indeed, in the first report of this trial (4-year follow-up), the OS difference between the two arms was not statistically significant [4]. In a subsequent report (5-year follow-up), the authors began to observe a significant survival difference in favor of the tamoxifen arm as well as a similar difference in the subset of patients who had relapsed [5]. However, as the survival estimates of this subset analysis were calculated from the time of randomization, this could also potentially be confounded by heterogeneity in the duration of the adjuvant endocrine therapy between study arms.

These challenges are not unique to the current study, but would be less of an issue in interpreting the initial results of the SOFT/TEXT trials (median follow-up 5.6 years) where treatment is given for the standard 5 years. This may however confound longer follow-up results as extended tamoxifen beyond 5 years becomes more widely adopted.

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Sunitinib 2 weeks on, 1 off: strengths and weaknesses

We read with great interest the article by Kalra et al. in this journal, where authors reviewed the available data on alternate sunitinib schedules for treatment of metastatic renal cell carcinoma (mRCC) [1]. Mainly, we focused on the use of the 2 weeks on, 1 off schedule, which has received large consensus among oncologists treating mRCC in recent years due to (i) the reduction of adverse events compared with the standard schedule of 4 weeks on, 2 off and (ii) the promising data in the overall disease control and outcome.

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We agree that use of this schedule may represent a step before dose reduction in patients who have experienced dose-limiting toxicity, especially those who experience the onset of toxicity during the third and fourth week in the 4 weeks on, 2 off schedule. On the other hand, caution should be exercised when patients experience toxicity in the first 2 weeks of therapy with a standard schedule, in which a dose reduction to 37.5 mg/day with the 4 weeks on, 2 off schedule remains the standard of care.

Regarding data on patient outcome, these should be handled with care, bearing in mind that patients treated with the 2 weeks on, 1 off schedule in retrospective series received the new schedule just after the occurrence of dose-limiting toxicities such as ‘hand–foot syndrome’. It has been reported in a previous article in this journal that several sunitinib-related toxicities (e.g. arterial hypertension, hand–foot syndrome, hypothyroidism) may have a predictive and prognostic role in mRCC patients [2].

Moreover, a retrospective study carried out on an Italian cohort of more than 200 patients treated with alternative schedules of sunitinib reported an improved safety profile and a median treatment duration (TD) and a median progression free survival (PFS) of 28.2 and 38.6 months, respectively, in patients who started with a 4 weeks on, 2 off schedule and shifted to 2 weeks on, 1 off after a median period of 4.3 months. On the other hand, in patients who immediately started with a 2 weeks on, 1 off schedule, a median TD and PFS of 7.8 and 9.6 months, respectively, was reported [3].

Considering its retrospective nature, this study, similarly to others reviewed by Kalra et al. cannot prove that a 2 weeks on, 1 off schedule is more active compared with the standard one, but confirms that patients such as those who experience treatment-related toxicities might have a better outcome. In addition, it should be taken into account that the overall survival rate may be conditioned by the duration of the first-line therapy [4]; therefore, patients who change schedule during the treatment may have a longer survival compared with those that start with the alternative one.

Finally, alternative 2 weeks on, 1 off schedule should not be used in all patients who experience ‘dose-limiting toxicity’ but only for patients who had ‘schedule-limiting toxicities’ during the third and fourth week of treatment in order to maintain dose intensity. At present, considering the lack of data, clinicians should avoid the use of the 2 weeks on, 1 off schedule at the beginning of therapy outside of a clinical trial.

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Alternative sunitinib schedules in metastatic renal cell carcinoma and the RAINBOW study

Kalra et al. recently published in Annals of Oncology a review about alternative sunitinib schedules in patients with metastatic renal cell carcinoma [1]. In particular, we appreciated their impressive analysis of the sunitinib pharmacokinetic and pharmacodynamic data carried out by the authors and the consequent suggestions for schedule modification in respect to dose reductions. These data were integrated with a review of the available clinical data.

In the Methods section, the authors reported that a literature search was carried out in the Medline database and supplemented by searches of the published abstracts of major meetings of the American Society of Clinical Oncology and European Society of Medical Oncology; only studies reporting phase I trials and retrospective cohorts with <20 patients were excluded from the review [1].

At the 2014 ASCO Genitourinary meeting, we presented the results of a large retrospective multicenter study which evaluated safety and outcomes of the alternative 2/1 schedule in 249 patients from 24 centers, 208 cases who started sunitinib on the standard 4 weeks on/2 weeks off schedule and thereafter switched to the 2/1 schedule for relevant toxicities and 41 who started first-line sunitinib with the 2/1 schedule because of suboptimal clinical conditions (Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: The RAINBOW study) [2]. We reported the significantly improved safety profile observed and the potential relevant methodological biases deriving from such a study.

We regret that our study, currently the largest experience about the 2/1 schedule, was not reviewed by Karla et al. in their review, although it clearly meets in the study definition provided by authors for data search in the Methods section.

The results of our study, although retrospective, may significantly contribute to a correct evaluation of the pros and cons of the 2/1 schedule modification, thus overcoming some of the limits deriving from the review: limited number of patients analyzed in each study and data deriving from single-center experiences.

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