Adverse events with everolimus in BOLERO-2

Rugo et al. recently reported on the 18-month median follow-up treatment-emergent adverse events (AE) with the use of 10 mg everolimus added to exemestane for metastatic estrogen receptor (ER)-positive breast cancer in BOLERO-2. The conclusion from the paper was that AEs with everolimus are mild to moderate and manageable with dose reductions that resolved with resumption of full dosing and age-independent treatment interruptions that were short lasting (median of 7 days). Grade 3 or 4 AEs and treatment discontinuation due to toxicity were uncommon.

More in detail reading this [1] and two other recent papers from the same 18-month median time of data cutoff in BOLERO-2 show less reassuring data for safety [2, 3]. Dose reduction or interruptions for AE appeared in 62.4% of everolimus users [1, 2] and only a minority re-escalated to the full dose (8%). Even at the reduced dose of 5 mg, dose reductions occurred in 34%. Grade 3 or 4 AEs were higher than what the authors stated as ‘uncommon’. A higher proportion of patients in the everolimus plus exemestane arm had treatment-related grade 3 or 4 AE (38.8%) compared with patients receiving placebo plus exemestane (8.4%) [2]. Although the abstract stated three times more discontinuations in the exemestane–everolimus (9%) than exemestane–placebo arm (3%), the text reads that AEs led to a 26% rate for permanent everolimus discontinuation [1]. On-treatment severe adverse events and deaths were also not mentioned in this AE paper.

The authors also reported that dose reduction and treatment interruptions were age-independent but previous papers showed age to be important for safety. With an age cutoff at 65 years, consent withdrawal, which in general reflects AEs, appeared in 13.8% of elder everolimus users, whereas this happened in 6.8% of younger users [3]. Permutt, permanent study treatment discontinuation due to an AE in the everolimus plus exemestane group for ‘both’ therapies was 15.9% in the elderly versus 4.5% in younger [3]. The rate of treatment-emergent AEs resulting in permanent everolimus discontinuation were 33% and 17% for those ≥65 and <65 years, respectively. On-treatment deaths with AEs as primary cause adjusted for treatment exposure were also more likely in the elderly [3].

Despite AE-related everolimus dose reductions, interruptions and discontinuations, a significant improvement in efficacy was seen with the introduction of everolimus for ER-positive metastatic breast cancer [2, 4]. It would be interesting to see efficacy data (progression-free survival, overall survival) by AE or toxicity. If toxicity predicts efficacy, clinicians and patients will be more eager to continue therapy but if on treatment toxicity hampers efficacy, predictors for side-effects beyond age should be explored to improve the benefit from this successful but also toxic drug.

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In reply to Gandaglia et al.

The recent paper by Gandaglia et al. evaluated the 8-year cancer-specific mortality (CSM) associated with intensity modulated radiation therapy (IMRT) in 19 064 patients with prostate cancer (PCa) [1]. Their complex and elegant matched pair analysis compares 9532 patients treated with IMRT and 9532 patients submitted to initial observation in the period 2001–2007. The authors conclude that IMRT is associated with lower CSM, but this gain is observed only in high-risk group patients. These results are somewhat analogous to the effect seen for surgery over watchful waiting especially in non-low-risk patients, recently reported by Bill-Axelsson et al. [2].

The major interest of this article is that it is the first published study clearly showing better CSM for PCa patients treated with IMRT. The message brought to the scientific community via a highly accessed oncology journal sounds like a positive input in favour of the use of radiotherapy over observation in PCa patients, particularly if delivered with the modern technique of...
IMRT. Up to now, no randomized, controlled phase III trials comparing IMRT against observation or older radiotherapy techniques are available. The absence of randomised data does not imply the absence of evidence: indeed other forms of comparative effectiveness research such as the proposed propensity-matched population-based analysis using SEER-Medicare database can inform clinical practice as well, provided that this methodology adhere to strict criteria. Despite that, comparisons presented and discussed in this article present, in our opinion, some important limitations which might have affected the proposed title and conclusions.

First, the prescribed radiation dose was not reported, and it was not included as covariate in statistical analysis. This information has always a crucial role in the interpretation of the results of studies concerning radiotherapy, in particular for high-risk PCa, where higher doses are needed and recommended [3]. IMRT is a sophisticated technique allowing dose escalation, while maintaining equal (or reducing) toxicity, when compared with standard 3D conformal technique [4, 5]. The absence of any information about dose prescription, when IMRT is the key point of the data interpretation, makes impossible to discern whether improved outcomes are related to IMRT by itself, rather than its inherently associated capability of allowing dose escalation.

Secondly, 52.6% of the IMRT population also received androgen deprivation therapy (ADT, versus 26.4% in the observation group), but no further data as the duration time, the type of drug and the category risk of patients receiving it are reported. Moreover, ADT was not considered as covariate in statistical evaluation. ADT has already showed a major impact on the overall survival of intermediate and high-risk PCa [3], and then it could potentially influence the results, in particular for the population that seem to benefit from IMRT. This is a crucial factor able to clearly affect the conclusions of the study.

Lastly but not least, it is difficult to share the decision of grouping low- and intermediate-risk patients, also looking at the recent data by Bill-Axelson et al., showing no impact of surgery on low-risk PCa. Indeed, a potential impact of radiotherapy could not be excluded also in this population of patients and, in the era of the active surveillance, it is important to state which patients would really benefit of radical treatments.

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In reply to the letter to the editor ‘in Reply to Gandaglia et al.’ by De Bari et al.

We thank De Bari et al. [1] for their thoughtful comments regarding our recently published study [2], which shows that intensity modulated radiation therapy (IMRT) leads to a survival benefit only in patients with high-risk prostate cancer (PCa). Of note, another relevant finding of our investigation was that IMRT did not result in improved cancer-specific survival in patients with low- and intermediate-risk disease compared with their counterparts receiving initial observation at 8-year follow-up [2].

As elegantly noted by De Bari et al. [1], a certain number of limitations in part affects the validity of our findings. For example the nature of our large contemporary cohort of patients prevented us from adjusting our models for treatment characteristics such as the prescribed radiation dose, which has been shown to impact on oncologic outcomes after treatment [3]. However, we should underline that all the patients included in our study were treated in contemporary years over a relatively short time period and, thus, they might ideally have received similar doses during IMRT. Nonetheless, further well-designed studies adjusting for this covariate are needed to confirm our findings.

Additionally, although our analyses were adjusted for the administration of androgen-deprivation therapy (ADT) and baseline disease characteristics, the lack of data on the duration of ADT and the grouping of low- and intermediate-risk patients limit the validity of our findings. However, to date, there are no level-1 data that show a survival benefit in patients treated with ADT, along with radiation. Such benefit is usually observed only in patients with high-risk PCa [4]. In consequence, it is unlikely that this lack of adjustment has biased our results, especially in the low/intermediate PCa-risk group.

Despite these limitations, our study represents one of the first attempts to compare IMRT versus observation in PCa patients. Indeed, since its introduction IMRT underwent a rapid (and uncontrolled) diffusion, even in the absence of solid data from prospective randomized trials assessing its oncologic efficacy. Nowadays, this approach represents the most commonly carried out treatment modality for patients with clinically localized PCa [5, 6]. However, advanced treatments, such as IMRT, are increasingly used in patients with...