Commentary

Concurrent or sequential letrozole with adjuvant breast radiotherapy

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Bourgier *et al*. (1,2) performed a thoughtful randomized clinical trial in the hopes that it would shed light on a clinically relevant topic, that lacks good evidence—what is the ideal sequence of endocrine therapy (ET) and radiation (RT) in women who receive breast conserving therapy for early stage hormone-receptor positive breast cancer? Moreover, the investigators also sought to identify a biomarker for radiation-induced subcutaneous fibrosis (RISF), using cutting edge for a translational science.

Hormone-receptor positive breast cancer is the most common sub-type (as opposed to hormone-receptor negative), and as a result, ET (tamoxifen and aromatase inhibitors) and RT are often given in the adjuvant setting as both have been independently proven to reduce the risk of breast cancer recurrence and death (3-5). Furthermore, in low-risk breast cancer patients, the combination of both adjuvant treatments have shown a statistically significant reduction in ipsilateral breast cancer recurrence (ET: 4.1% versus breast RT+ET: 1.3%, P=0.0002) (6). While many studies have attempted to define a low risk population that might benefit from omitting RT (6-9), controversy still remains (10) and as a result, both treatments are still given to a large population of breast cancer patients (11). This makes the trial by Bourgier *et al*. (1,2) especially relevant to a large community of patients, since hormone positive breast cancer is commonly seen in the postmenopausal population, who are often treated by ET and RT (3-5).

The sequencing of ET and RT has theoretical oncological and cosmetic ramifications. ET is thought to arrest the hormone-dependent-cancer cells in the early G1 phase of the cell cycle, which happens to be the most RT-resistant phase; RT's lethal effects are most efficient at the G2/M cell cycle phase. Therefore, concomitant treatment can potentially compromise the efficacy of RT (12). However, clinical studies have not clearly demonstrated an inferior outcome for concomitant HT and RT (1,2,13-17). Also pre-clinical studies, including by Azria *et al*. (18), found conflicting results, indicating that there may be various pathways that influence outcome. This might contribute to the fact that even though Azria (18) showed that letrozole sensitized human breast cancer cell-line to RT, in the clinical setting the investigators did not observe differences in oncological outcomes at a median follow up of 74 months (1). As a phase II design, low risk breast cancer, small number of patients and short follow up, the study might have not been powered to detect such differences (1).

The primary emphases of this current report include RT induced-toxicities, quality of life (QOL), cosmetic outcome and potential biomarkers for RT-induced normal tissue injury. RT-induced subcutaneous fibrosis did not differ between the two study arms. While lung toxicity was assessed by repeated computed tomography (CT) and did not differ between the groups, cardiac toxicity was assessed according to CTCAE v 3.0. Although no symptomatic cardiac toxicity was reported, the information provided by the authors does not enable the reader to reach a conclusion about the validity of the cardiac reported results (number of left breast cancer treated, RT techniques to reduce cardiac dose). As we previously published (19), there are a few RT techniques that may minimize cardiac exposure and better/more sensitive measures to asses acute and late cardiac toxicity (19). QOL in this trial was assessed using QIC-C30/BR-23 EORTC, which might not be the best tool to capture ET and/or RT associated QOL issues.

The investigators should be congratulated for performing their thoughtful translational studies. Both radiation-induced lymphocyte apoptosis (RILA) and single-nucleotide polymorphisms (SNPs) were evaluated to potentially identifying a sub-population of patients that might be more subjected to RT-associated toxicity. RT-induced lymphocyte apoptosis was shown to be a potential biological dosimeter and the concept of the differences in RILA among patients and RT-associated toxicity is intriguing. The investigators found that among all the risk factors studied, RILA was significantly predictive of grade >2 fibrosis. Although the number of patients who had >2 fibrosis was low (n=5), these findings are thought-provoking and should be further evaluated. The association between lung V20, V30 and RISF grade >2 might be attributed to large separation (thus more skin exposed) (1).

The wide-genome association study (GWAS) is a well-known international effort to identify SNPs associated with RT toxicity (20). This type of international collaboration should also be commended, as large numbers of patients are needed in order to "overcome" the wide diversity between patients and obtain clinical validity. It takes considerable effort to examine many genetic variants in different individuals to see if any variant is associated with RT induced toxicity. The investigators report that two SNPs were identified as being significantly associated with RILA, again exciting new evidence that should be further evaluated.

We agree with the authors' conclusions that it seems that letrozole can be given safely, concomitantly with adjuvant breast RT. However, the true impact of this sequence might be only demonstrated in a larger population study with longer follow-up.

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Footnote

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