



Concurrent or sequential letrozole with adjuvant breast radiotherapy: primetime for personalized radiation oncology

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We would like to thank both Kaidar-Person (1) and Meattini (2) for their very constructive and positive commentaries. As mentioned by Kaidar-Person (1), efficacy of adjuvant breast cancer radiotherapy after breast conserving surgery is well established since many years by reducing both breast recurrences and breast cancer death (3). In addition to radiation therapy, endocrine treatment [tamoxifen and aromatase inhibitor (AI)] also significantly reduced recurrence and 10-year breast cancer mortality rate (4). The ideal sequence of endocrine therapy and radiation (concurrent or sequential use) was prospectively assessed in the CO-HO-RT randomized study (5). This clinical trial was designed to evaluate the risk of radio-induced subcutaneous fibrosis (RISF) occurrence (primary endpoint) between the two arms but no significant RISF difference was observed between concurrent or sequential arms with long-term follow-up (6). Therefore, even though letrozole showed radiosensitization properties regarding human breast cancer cell-lines (7), some recent preclinical data displayed a reduction of lung fibrosis when combined to radiation (8). Indeed, clinical data confirmed that concurrent AI and radiotherapy do not increase late toxicities (6). In addition, a large and exhaustive literature review was recently published and reported no difference in esthetic outcome or toxicities between sequential or concomitant endocrine treatment, regardless tamoxifen or AI use (9).

The keypoint of the COHORT is that only patient with low radio-induced lymphocyte apoptosis values presented high grade of RISF (6). In that trial, RILA was a stratification factor to avoid imbalance between

the two randomization arms considering that intrinsic radiosensitivity may influence the impact of a systemic therapy delivered concomitantly with radiotherapy. The RILA predictive assay has been developed by Ozsahin *et al.* (10) as a rapid test for intrinsic radiosensitivity (results within 24 hours). Independent retrospective (11-15) and monocentric prospective studies (16,17) showed that low RILA values were significantly associated with the risk of RISF occurrence. In breast, we reported 12 years ago (18) that the use of tamoxifen enhanced breast fibrosis only in hyper-reactive patients (i.e., patients who presented a low RILA value). Even though CO-HO-RT trial was not designed to assess RILA as a RISF predictive factor, a prospective and multicentric study (19) recently confirmed that RILA can be used as a predictive RISF biomarker. Only few genetic specific variants (20) or genome-wide association study (GWAS) identified and validated a RISF biomarker among multiple single polymorphism nucleotides (SNPs) or genes (21). In the CO-HO-RT study (6), a GWAS analysis was performed to identify SNPs that would improve identification of patients at high risk of severe RISF. With a short sample size, no SNP was significantly related to fibrosis but 2 SNPs (rs1182531 and rs1182532, located within the *PHACTR3* gene on chromosome 20q13.33) were significantly associated with apoptosis leading to a better understanding of the RILA assay.

As mentioned by Meattini *et al.* (2), inflammatory and immune responses occurring after ionizing radiation stress are involved in normal tissue response. There is a need to better understand molecular mechanisms which contributes to fibrosis state, from acute to late radio-induced side

effects. Our present results provide innovative perspectives for further investigations.

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