Commentary

Concurrent or sequential letrozole with adjuvant breast radiotherapy

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We have read with interest the final results of the CO-HO-RT phase II trial, recently published by Bourgier and colleagues (1). In brief, 150 patients affected by stage I-II breast cancer (BC) were randomized to receive either concomitant or sequential letrozole and adjuvant radiotherapy (RT) after breast conservative surgery. Furthermore, 121 patients were tested for radio-induced lymphocyte apoptosis (RILA), and single nucleotide polymorphisms (SNP) related to radio-induced subcutaneous fibrosis (RISF). Authors did not find differences in terms of safety between concomitant or sequential letrozole and RT, but translational sub-analysis identified a correlation between RILA and RISF, with a significantly lower value of RILA in patients with RISF grade ≥2 compared to RISF ≤1 (6.9% *vs.* 13%; P=0.02). Moreover, two SNP located within phosphatase and actin regulatory protein 3 (*PHACT3*) gene resulted significantly associated with RILA.

To our knowledge, the same group previously published the most important study about the radio-sensitizing effect of letrozole in 2005 (2); in this study Michigan Cancer Foundation-7 (MCF-7) human BC cells were incubated with androstenedione (ASD) in the presence or absence of letrozole, and irradiated with doses ranging from 0 to 4 Gy. Results showed that the survival fraction at 2 Gy was 0.66 for RT alone and 0.44 for RT plus letrozole (P=0.02). This observation, together with the results from the CO-HO-RT study, seems to suggest the biological efficacy and clinical safety of concomitant letrozole and RT.

PHACTR genes (PHACTR 1-4) codify for a family of highly conserved phosphatase and actin regulatory proteins. Data from literature showed that SNP on a locus corresponding to PHACTR 1 (Chr6p24.1) were associated with atherosclerosis (3); moreover proteins of the PHACTR family seem to play a role in angiogenesis and to be implied in tube formation and lamellipodial dynamics, with the control of Vascular Endothelial Growth Factor-A 165 (VEGF-A 165) and its interaction with Neuropilin-1 (NRP-1) and Vascular Endothelial Growth Factor-R1 VEGF-R1 (4).

Furthermore, studies on the biological function of these proteins showed that selective inhibition of the interplay between VEGF-A factor and PHACTR-1 regulators triggered the expression of Metalloproteinase (MMP) regulators and some inflammatory effectors such as Thrombin and Thrombin receptor 1 (PAR-1) involved in atherosclerosis process (5).

PHACTR genes showed to have also a relationship with Protein phosphatase 1 (PP1) activity induction and nitric oxide synthase regulation (6,7). This could suggest that *PHACTR* genes could be implied in a complex mechanism comprehending MMP regulation, inflammatory response and oxidative stress regulation, influencing the micro-vascular environment and the fibrotic response to RT; therefore the relationship with RILA could be a part of a wider network.

As underlined by Azria and colleagues (2), other SNP associated with RISF was recently identified on thioredoxin reductase 2 (*TXNRD2*) gene, a mitochondrial enzyme implied in reactive oxygen species scavenging (8), suggesting the pivotal role of oxidative stress in this kind of tissue fibrosis.

Another important role of PHACTR proteins seems to be related to cytoskeletal function, influencing cell motility and morphogenesis (9,10), we think that this is consistent

with the association observed in the study by Azria *et al.*, considering that these functions are fundamental for all cells implicated in fibrotic process (i.e., macrophages, fibroblast).

Anyway RILA showed to be related to RISF, thus fibrosis seems to be related also to lymphocyte activity, and it should not be considered only as a passive response to tissue damage, but rather an effect of active tissue response to radiation injury.

Results from the observation by Azria *et al*. showed that RISF ≥3 was significantly associated with rs9421747 SNP on chromosome 10q11.22; interestingly, loss of this chromosome region was detected as a recurrent genomic imbalance using a 250k GeneChip® SNP array on 47 peripheral T cell lymphomas (11), suggesting that this region could be important for T cell lymphocyte proliferation control. SNP on 10q11.22 could be actually implied in a pro-survival mechanism of T cell lymphocytes, explaining the presence of a subgroup of patients with different levels of RILA, influencing fibrotic response to RT.

These considerations strengthen the relationship found by Bourgier and colleagues (1), suggesting that T cell lymphocytes could cooperate in the regulation of pro-inflammatory response triggered by RT. The authors underlined that in the letrozole-RT sequential group, significantly more women smoked or were ex-smokers (P=0.03), and we think that this is an important issue to consider. In fact, immune response and cytokines production of peripheral blood mononuclear cells is influenced by smoking habit, probably through mechanisms implying alterations in oxidative stress (12). Thus, the imbalance of this feature between the two studied groups could affect the abovementioned mechanism and change the microenvironment response to RT, probably influencing the response of normal tissue. Moreover we should expect that smoke habit could increase the fibrotic response to RT, inducing a more pronounced fibrotic response in patients treated sequentially with letrozole, and constituting a possible study bias.

Inflammatory and immune response to radiation injuries, together with oxidative stress, represented a complex mechanism probably affected by several external stresses.

Explaining the relationship between fibrotic response, and SNP on PHACTR proteins and presence of RILA is particularly interesting, beyond the practical aspects concerning the concomitant or sequential use of letrozole and RT.

The comprehension of molecular and immune pathways lying behind RISF and normal tissue tolerance to RT is of outstanding importance, and the paper by Bourgier and colleagues in our opinion evidenced promising data about this issue, opening exciting perspectives for further investigations.

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