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LETTER TO THE EDITOR

Pre-radiotherapy identification of individual genomic profile to avoid, by resort to customized radiosensitizers, the risk of radioresistance development in patients with localized prostate cancer

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To the Editor,

In the Bristow et al[1] study, prostate cancer (CaP)-related genomic predictors of prognosis and radiotherapy response are carefully taken into consideration, together with hypoxia-affected cancer microenvironmental conditions. Particularly, pre-treatment DNA/RNA-based genomic tests as well as assays reflecting hypoxia-influenced cancer metabolism behaviour are the subject of a proven thorough research.

Looking to further CaP genomic profile assessments to reach a more customized radiation therapy against a possible development of cancer radioresistance, other approaches may be highlighted. The identification, indeed, of gene aberrations responsible for either the hyperactivation of cancer cell proliferation signalling pathways, such as phosphatidylinositol 3-kinase (PI3K)-Akt/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK) and signal transducer activator of transcription (STAT), or, instead, the evasion of apoptosis signalling pathway—from caspase sequence machinery to proteolytic cleavage of poly-adenosine diphosphate ribose polymerase-1 (PARP-1) with following DNA fragmentation—may lead to them being targeted by specific radiosensitizer agents, among which NVP-BEZ235 or SB203580 (respectively, inhibitors of the PI3K-Akt/mTOR or MAPK pathways), AG490 to block STAT3, HA14-1(opposed to the antiapoptotic Bcl-2), olaparib as a PARP-1 blocker and LCL521/385 to target acid ceramidase proteolytic degradation promoters.[2,3]

Regarding genomic predictors of radiation therapy response, a particular significance is today also recognized with regards to the prostate cancer stem cell (PCSC) genes, that are often responsible for the CaP radio- and/or chemoresistance development by enhancing cancer cell proliferation and supporting cancer cell death evasion. Indeed PCSCs, by ATR (ataxia telangiectasia-mutated/Rad-related kinase proteins) gene-mediated DNA repair mechanisms, make sure of their own survival against ionizing radiation. Moreover, the specific gene mutation-dependent overactivation of PCSC self-renewal pathways—such as Wnt/β-catenin, Hedgehog and Notch pathways—play an important role in facilitating the radioresistance development. In this regard, perifosine, besides inhibiting Akt/cytoskeletal signalling pathway, can also block the Wnt one following tumour radiosensitization. In addition, CXCR4 (CXC motif receptor 4) chemokine has been recently identified as a biomarker for both drug- and radioresistant cancer stem cells, given that its interaction with the specific ligand CXCL12 can protect them from anticancer agents and radiation. It follows that a feasible block of such interaction could represent a promising chance to improve the CaP radiation therapy.[4]

Intriguingly, the inherited variation of single nucleotide polymorphism (SNP) in ribonuclease L (RNASEL) gene—rs 12757998 variant allele in chromosome 1q25—can affect organ-confined CaP outcome after external beam radiation therapy, given its association with increased circulating C-reactive protein and interleukin-6 that play a potential role in inflammatory response to radiation following tumour cell apoptosis. Hence, low inflammatory RNASEL SNP rs 12757998 gene-dependent protein levels seem to be responsible, instead, for the CaP cell apoptosis decrease-induced radioresistance.[5]

With high esteem towards Bristow et al's[1] research work, it is foreseeable that more and more detailed pre-radiotherapy CaP genomic profile assessment—in the field of properly customized healthcare—might allow, by a possible resort to suitable personalized radiosensitizer measures, favourable radiation therapy optimization opportunities to be reached.[6]

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