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focus on

Molecularly targeted radiosensitization chances towards gene aberration-due organ confined/regionally advanced prostate cancer radioresistance

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SUMMARY: **Molecularly targeted radiosensitization chances towards gene aberration-due organ confined/regionally advanced prostate cancer radioresistance.**

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Considering that the prostate cancer radioresistance occurs in a significant percentage – as 20-40% of prostate cancer (PCa) patients undergone external beam radiation therapy developing, within ten years, recurrent and more aggressive tumor – the resort to customized radiosensitizer measures, focusly targeting PCa radioresistance-linked individual molecular aberrations, can increase the successful outcomes of PCa radiotherapy.

KEY WORDS: Prostate cancer - Urology - Radiation therapy - Radioresistance - Molecular biology.

Introduction

Despite external beam radiation therapy (EBRT) delivery technological advances – from intensity modulated therapy to tomotherapy and image-guided robot 6D radiotherapy, allowing high energy radiation delivery meanwhile minimising side-effects – the prostate cancer (PCa) biochemical/clinical relapse percentage remains nowadays high (post-EBRT PCa recurrence at 20-40 %) (1-3).

As personalized medicine-related pharmacogenomic approaches are today the individual gene aberration molecularly targeting radiosensitizer measures to either prevent or overcome the prostate cancer radioresistance occurrence (1-7).

Current research focus and forecast of advances in tumor radiosensitization

Unfortunately, it seems that a certain reluctance to meet with such novel knowledges might at times occur probably on the basis of a poor grounding in oncogenetics and molecular biology. So far, the field of radioresistance conditions is often restricted to tumor microenvironmental hypoxia as low levels of reactive oxygen species (ROS) notoriously driving the cancer cells, by the development of the antiapoptotic hypoxia-inducible factor 1 (HIF 1), to radiation refractoriness onset. However, such radiobiological feature is so common of solid tumors – as it carefully detectable today by real-time mapping pO_2 tissue fluctuations with resort to electron paramagnetic resonance and, in case of intraoperative radiotherapy, to phosphorescent ruthenium-nitroimidazole optical imaging – that it shouldn't be defined as a genomic individual condition involving really customized radiosensitizer approaches (8, 9).

It's intriguing, instead, that pre-radiotherapy individual genomic profile findings may lead to identify cancer cell growth/apoptosis pathway individual gene aberrations that can cause the radioresistance, so this condition should wisely imply the resort to customized molecularly targeted radiosensitizer agents (10). Besides the outlined conditions (Table 1), it has to be taken into consideration some PCa cell radioresistance biomarkers, among which particularly EMT (epithelial-mesenchymal transition with down-expression of E-cadherin compared with mesenchyme-peculiar expression of vimentin) and CD44-variant 6 marker, whose small interfering RNA (siRNA)-mediated knock-down can suppress, by deactivation of PI3K-Akt/mTOR and Wnt/βcatenin signaling pathways, the PCa cells growth,

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TABLE 1 - PROSTATE CANCER RADIOSENSITIZERS TOWARDS INDIVIDUAL RADIORESISTANCE CONDITIONS.

Gene aberration-related radioresistance	Customized radiosensitizers
Cancer cell growth pathway hyperactivation:	
- Phosphatidyl inositol 3-kinase(PI3K) -Akt/mammalian target of rapamicin (mTOR) pathway.	- NVP-BEZ 235 or NU7 441,as dual ATP-competitive PI3K and mTOR blockers. NVP-BEZ also inhibits HIF-1. Zotarolimus, as analogue of rapamicin,blocks mTOR.
- Janus tyrosine kinase - Signal transducer activator of transcription (Jak-STAT) pathway .	- AG 490, as a suitable specific blocker of Jak-STAT pathway, can radiosensitize the prostate cancer cells. Ruxolitinib and fludarabine are respectively selective inhibitors of Jak1/2 and STAT3.
- Interactions between overexpressed MDM2 (mouse double minute 2) and p53 with subsequent lack of p53 normal function, hence enhancement of cancer cell growth.	- Nutlins, as cis-imidazoline analogs, may prevent p53-MDM2 interactions, so inhibiting cancer cells growth meanwhile restoring tumor radiosensitivity. MDM2 antagonist Nutlin-3 also facilitates apoptosis.
- Overexpression of HER2(Human epidermal growth factor receptor type2 of tyrosine kinase).	- Trastuzumab (Herceptin),by blocking HER2, inhibits PCa cell proliferation.
- Histone deacetylase (HDAC) epigenetic hyperactivity.	- SB939, as PCa cell HDAC inhibitor
Cancer cell apoptotic pathway evasion:	
- Suppression of apoptosis machinery by overexpression of antiapoptotic Bcl-2 gene.	- HA14-1 and ABT-263(Navitoclax), as inhibitors of Bcl-2,facilitate the apoptotic process.
- Suppression of proteolytic cleavage of poly(ADP-ribose) polymerase-1 (PARP-1),so preventing apoptosis-proper DNA fragmentation.	- Olaparib, veliparib, niraparib, as blockers of PARP-1, allow the cancer cell death, so it reaching the prostate cancer cell radiosensitization.
- Survivin gene overexpression, by interfering with caspase activity, supports cancer cell survival.	- YM155, as survivin inhibitor, acts as radiosensitizer of prostate cancer cells.
- Clusterin,as inhibitor of Bax proapoptotic activity,protects cancer cells from TGFβ-induced apoptotic mechanisms.	- OGX-011 antisense nucleotide ,by promoting a down regulation of clusterin expression, can restore cancer cell apoptosis and radiosensitivity.
- Ceramide accumulation-induced,by feed-back,ceramidase gene up-regulation leads ,in turn, to produce the ceramide catabolite sphingosine and its phosphorilated derivative sphingosine-1-phosphate, that may support activation of Akt pathway, with following cancer cell growth enhancement and radioresistance onset.	- LCL 521/385,as promoters of ceramidase proteolytic degradation, can mantain the ceramide-associated apoptotic process meanwhile radiosensitizing cancer cells. -Toremifene, as tamoxifen-like antiestrogen, is also an efficacious inhibitor of acid ceramidase activity.
In addition,some inhibitors of cytoskeletal signaling pathway,such as Akt blocker perifosine as well as both paclitaxel and epothilone B microtubule stabilizers , can accelerate the development of the cell apoptotic process.	
Cancer stem cell-related radioresistance:	
- Particular gene mutation-dependent over-activation of stem cell specific pathways – such Wnt/βcatenin- ,Hedgehog-and Notch signaling pathways – plays an important role in facilitating both self-renewal process and radioresistance onset.	- Perifosine, besides blocking Akt and PI3K, can also inhibit the Wnt signaling,with following restoration of tumor radiation sensitivity. Miltefosine,though like perifosine, isn't suitable as a radiosensitizer agent.
- CXCR4 (chemochine CXC of receptor 4),by interacting with its ligand CXCL12, can cause both cancer stem cell chemo- and radioresistance.	- Foreseeable block of CXCR4-CXCL12 interactions should represent a promising opportunity to refine the prostate cancer radiation therapy.

so increasing their radio- and chemosensitivity (11, 12).

The discovery of PCa stem cell (PCSC)-peculiar radioresistance genes, among which the PCSC 1 and PCSC 2 RAN (Ras associated nuclear protein) ones, involved in DNA synthesis and cell cycle promotion, allow a further explanation of post-radiotherapy PCa recurrence, that's why they may be an important target in the field of radiosensitization measures (13).

It is emerging from a recent study (14) that the chronic stress/obesity-dependent norepinephrine or epinephrine-triggered enhancement of sympathetic sygnaling, mainly involving prostate luminal cell β_2 adrenergic receptors, may support, together with PCa cell neuroendocrine transdifferentiation, the Bcl 2-mediated antiapoptotic effects and the radioresistance onset. It follows that the use of β_2 adrenergic receptor antagonists – among which ICI 118,551 hydrochloride, $C_{17}H_{27}NO_2$ HCL – could play a customized role to overcome the PCa radioresistance, though ionizing radiation, as well as the androgen deprivation, may facilitate the PCa cell neuroendocrine transdifferentiation. As it's well-known, indeed, the ionizing radiation can increase both intranuclear phospho-CREB (cyclic AMP-response element binding protein) and cytoplasmatic ATF 2 (activating transcription factor 2), factors that may induce the NE-transdifferentiation by which PCa cells become radiation therapy resistant (14-16).

What's more, some blockers of cytoskeletal signaling pathway – such as the perifosine inhibitor Akt (also known PKB, protein kinase B) as well as microtubule stabilizer paclitaxel or epothilone B – can accelerate the development of cancer cell apoptosis, so it facilitating the prostate cancer cell radiosensitization (10).

On the basis of deepened radiobiological features – high linear energy transfer, radiobiological effectiveness, tumor dose delivery targeting with tumor/healthy tissue damage highly positive ratio – both hadron (proton/neutron) beam- and carbon ion radiation-therapy seem to successfully overcome some radioresistance classical conditions (PCSC-related risk, crucial α/β cancer cell radiation sensitivity ratio, etc) meanwhile better sparing pelvic organs in comparison with EBRT. Nevertheless, such hadron radiobiological features prove to be ineffective, in some ways, to overcome individual gene aberration-due prostate cancer radioresistance.

Conclusion

As a final remark, it is advisable to widen the research range of PCa radioresistance conditions beyond the hypoxia-dependent one, as they often implying quite individual gene aberrations towards which suitably tailored radiosensitizer approaches should be carried out.

Among further developments of customized radiosensitizers, just those molecularly targeting the identified PCa cell radioresistance-linked individual gene aberrations will enhance the PCa radiation therapy lasting effectiveness (1-7, 10-19).

Conflict of interest statement

No conflict of interests.

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