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Abstracts

Radiotherapy

THE DELAY TIME IN RADIOTHERAPY

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In radiotherapy center, the waiting time represents one of the most greater problems. The principal cause of this phenomenon is represented by a smaller offer in comparison to the demand. In fact, in these last years the application of radiotherapy is increased both for the most greater incidence of new cases of cancer and for a greater extension in the radiotherapy indications. The delay in the beginning of the radiant treatment has on the patient negative effects is direct (what the tumoral growth, the worsening of the symptoms, the psychological effects) both indirect effects like trips of the hope and pressure on the radiation oncologist, that can jeopardize the quality of the same radiant treatment. Numerous evidences have shown that the delay in to begin can influence the obtainable results with the radiotherapy, allowing the proliferation of clonogenic cells inside the target and consequently a diminution of the local control. Besides the delay in the beginning of the radiotherapy can influence negatively the process of onset of the metastasis. None of the numerous present evidences in literature on the influence of the delay of the radiotherapy and that they suggest the role of the delay of the radiotherapy in the increase of the risk of local relapse, it reaches the level of 'evidence-based medicine'. In fact anybody study show a clear relationship among cause and effect, besides none of these studies has been drawn to the purpose to verify if this relationship exists. It is reasonable however to think that, through the improvements reached in the knowledge of the tumoral progression in the patients waiting for radiotherapy, especially as it regards the patients affections from the head and the neck cancer, the delay of the I begin some radiotherapy is responsible of many local failures. Although the effects of the delay of the radiotherapy is not the same for all the tumors, the negative effects tied up to it, can frustrate the benefits effects reached by the technological advancements of the radiotherapy.

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OPTIMIZATION OF THE THERAPEUTIC INDEX THROUGH THE INTEGRATION AMONG TARGET THERAPY AND RADIOTHERAPY

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Until now, the majority of the cancer therapy have not been specific: not based on the tumour biology and associated to a meaningful toxicity. The classical radiobiology has furnished valid elements on the cellular kinetics, has furnished valid elements on the cellular kinetics, on the processes of reparation and damage of the DNA and on the biological basis of administration of the dose, putting the bases for the new radiobiology, regarding the interactions of radiation ionizing and molecular-targeted agents. In the last years the therapeutic approach to the tumour is changed: the target of the cancer therapies is not more directly the neoplastic cells but is directed against targets necessary for tumour cell growth and viability with little toxicity to normal cells compared to conventional cytotoxic agents (Fig. 1).

Moreover, the modern radiobiology it is turned toward the molecular biology, not more the DNA as target but not DNA targets: specific growth factor or signal transduction inhibitors, as CDK, PKC, EGFR, VEGF, FT, MAPK. The non-DNA targets they result effective in to determine the cellular death or to make the most sensitive cells to the radiations. In 2006, Bunn[1] reported that 'Targeted therapy and radiation may work together in two

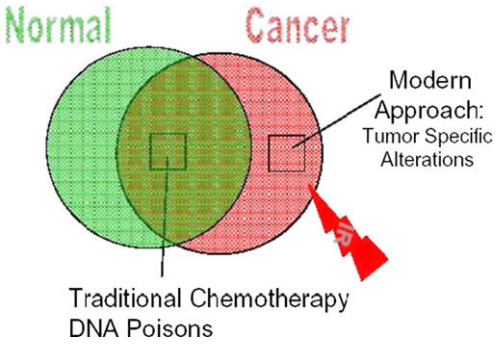

Fig. 1. The combination of targeted therapy and radiotherapy to treat cancer (Giaccia A. ASTRO 2007).

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ways, by increasing effectiveness of radiotherapy in local tumour and also a systemic effect by killing cancer cells outside the tumour site as well…. First, that novel (targeted therapy) agents in themselves do not cure the cancer, but, we have also learned that while these novel agents alone do not cure advanced cancer, they may have the ability to cure patients when combined with radiation or chemotherapy in earlier cancers. The epidermal growth factor receptor (EGFR), a member of the HER (erbB) family of transmembrane receptor tyrosine kinases, is overexpressed in the majority of solid tumours as non-small-cell lung cancers (NSCLC) or squamous cell carcinoma of the head and neck (SCCHN). EGFR may also play a role in cellular responses to chemotherapy or radiotherapy. The expression of EGFR and its ligands is upregulated by cells in response to irradiation, and the ability of cells to continue dividing and resist radiation-induced damage appears to be influenced by activation of the EGFR signaling pathway.[2,3]

An advantage of the combination among target therapy and radiotherapy it is that they each affect the cell growth cycle at different point. Chinnaiyan et al.[4] reported that radiation most commonly induces an arrest at the G2 point, while Erlotinib more strongly affects the G1 point resulting in an increase of the radiotherapy-induced apoptosis. In the phase III trial of Bonner et al.[5] the addition of Cetuximab to high-dose radiation for curative intent in patients with squamous cell carcinoma of the head and neck increased three-year survival from 45% to 55% ($P = 0.03$). The EGFR-targeted therapies and radiation further to arrest cell cycle progression at different checkpoints, when administered in combination produce enhanced antiproliferative activity, apoptosis induction, inhibition of DNA damage repair, and antiangiogenic and antimetastatic effects.[4,6–9] Data presented by Azria et al.[10] suggest that tumour radiation-sensitization through the inhibition of EGFR signaling could yield a therapeutic gain by increasing the locoregional control rate in patients with EGFR-overexpressing rectal cancer. With regard the relationship between radiation and antiangiogenic agents, the concept that attacking a tumour's supportive blood vessel network could offer a means of improving cancer cure rates has received a great deal of attention in recent years. Initially tumour growth depends upon its host for its blood supply.[3] But for growing beyond a certain size, angiogenesis is required (Fig. 2). The combination may produce a synergistic anti-tumour effect. The agents are divided, mainly, in two groups: (1) VEGF inhibitors (as the Semaxanib, used for advanced malignancies) and (2) Anti-VEGF and VEGFR Antibodies (as the Bevacizumab).

Enhancement of tumour response to radiation plus antiangiogenic agents has also been explained by an increase in tumour oxygenation after treatment. Indeed the application of vascular targeting strategies as adjuvants to standard therapeutic modalities may offers unique opportunities to develop even more effective cancer therapies. The non-DNA targets they result effective in to determine the cellular death or to make the most sensitive cells to the radiations. In conclusion, an only mechanism that conducts to the radiation sensitizing does not exist.

The mechanism of radioresistance or radiosensitization is complex and understanding different factors like the induction of apoptosis, effects on the regulation of the cellular cycle, the reparation of the DNA and the angiogenesis. Bentzen et al., unpublished data in 2005, have hypothesized that besides the steel paradigm other types of interactions exist, what biological cooperation, kinetic cooperation and normal tissue protection. The future directions of the radiobiology it is the use of therapeutic strategies that integrate the ionizing radiation in combination with one or more molecular-targeted agents There is immense potential for improving efficacy and diminishing toxicity through application of target therapy combined with radiations or chemoradiations. The future of cancer treatment is targeted therapy, and as brought from by Pegram et al.[11] '*Targeted therapy: Wave of the future*'. The purpose of the new treatments strategies and new drug to convert cancer into a chronic disease.

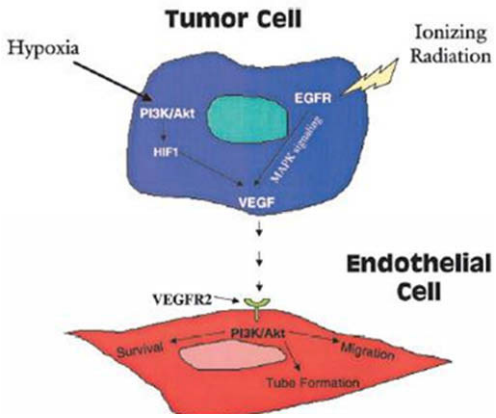

Fig. 2. Signaling mechanisms involved in VEGF induced tumour angiogenesis (by Wachsberger P, Burd R, Dicker AP; 1957 and Clin Cancer Res 2003:9;1957–1971).

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