Combining Immunotherapy and Radiation for Prostate Cancer☆

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Abstract

Radiotherapy has conventionally been viewed as immunosuppressive, which has precluded its use in combination with immunotherapy for prostate and other cancers. However, the relationship between ionizing radiation and immune reactivity is now known to be more complex than was previously thought, and data on the use of radiotherapy and immunotherapy are accumulating. Herein, we review this topic in the light of recently available data in the prostate cancer setting. Recent research has shown no significant lymphopenia in patients undergoing radiotherapy for high-risk adenocarcinoma of the prostate. In addition, emerging evidence suggests that radiotherapy can have immunostimulatory effects, and that tumor cell death, coupled with related changes in antigen availability and inflammatory signals, can affect lymphocyte and dendritic cell activation. Initial studies have focused on combinations of tumor irradiation and immunotherapy, such as the autologous cellular immunotherapy sipuleucel-T and the monoclonal antibody ipilimumab, in metastatic castration-resistant prostate cancer. These combinations appear to have clinical promise, and further investigation of the potentially synergistic combination of radiotherapy and immunotherapy is continuing in clinical trials.

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Introduction

Radiotherapy has historically been thought of as immunosuppressive and therefore not appropriate for combination with treatments that act on the immune system. However, this view of radiotherapy might be overly simplistic, and a growing body of evidence suggests that ionizing radiation can be immunostimulatory. This opens up opportunities for combining radiotherapy with cancer immunotherapies, which are approved or under investigation for various malignancies including prostate cancer. Clinical data on the use of radiotherapy with immunotherapy, both together and sequentially, are accumulating. In this review we consider recent advances that challenge widely held views, not only on the effects of radiotherapy but also the potential synergy between radio- and immunotherapeutic approaches.

Effects of Radiotherapy on the Immune System

The accepted rationale for using radiotherapy in cancer is underpinned by tumor cell death and effects on tumor-associated stroma caused by DNA damage.[1] The conventional view is that rapidly dividing cancer cells are more sensitive to ionizing radiation than normal tissue, and therapeutic radiation is therefore applied to induce apoptosis and other forms of cell death within a defined area while minimizing toxic effects on normal tissue around the treatment field.[1,2]

Inevitably, irradiation of living tissue involves damage to that tissue, whether it is tumor tissue, normal host stroma, normal host parenchyma, or leukocytes.[1] The attenuation of lymphocyte numbers by radiotherapy, as previously reported in patients undergoing treatment for gynecologic[3] or prostate[4] malignancies, might therefore be viewed as an adverse effect. The ultimate manifestation of this is seen in patients who undergo total body irradiation (as widely used in conditioning regimens for hematologic malignancies), who experience prolonged pancytopenia.[5] Studies have described reductions in numbers of T, B, and

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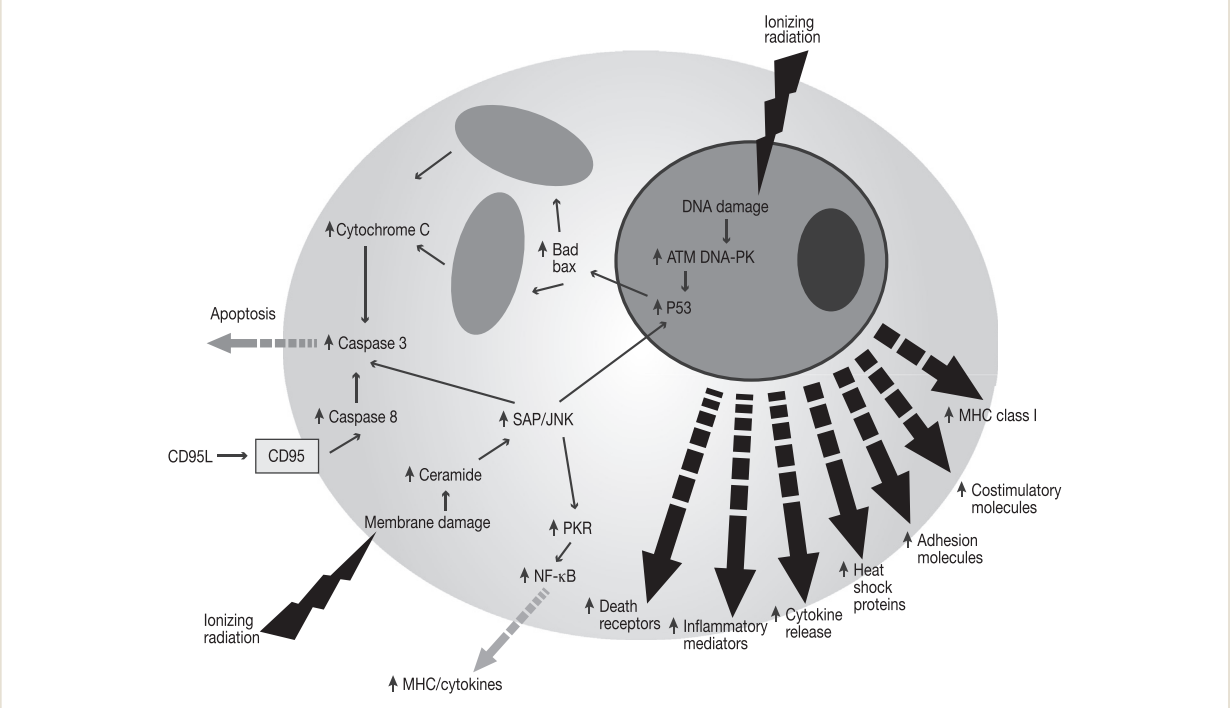
natural killer (NK) cells, apoptosis or alteration of antigen-presenting cells (APCs), including dendritic cells (DCs) and macrophages, apoptosis of lymphocytes, and changes to antigen expression on tumor cells after radiotherapy with doses from approximately 50 to 70 Gy.[3,4,6,7] Localized radiotherapy has reportedly resulted in significant reductions in lymphocyte levels in stage I to II prostate cancer or locally advanced gynecologic neoplasms.[3,4] Similarly, studies on radiotherapy in patients with stage I to III breast cancer have shown lymphopenia, low functional activity of NK cells, decreased monocyte phagocytosis, and decreased tumor necrosis factor (TNF)-α production.[7]

Observations such as these have contributed to the conventional view of radiation therapy as immunosuppressive, and it has therefore not been used with cancer immunotherapy. However, emerging data suggest that standard radiotherapy in high-risk prostate adenocarcinoma might not be as immunosuppressive as previously thought, nor the relationship between radiation and immune responses as straightforward.[1,8] The relative contributions and reactions of systemic and locoregional cell populations and the differing effects of dose and delivery methods might influence immune responses via a range of cellular mechanisms (Figure 1).[9]

Radiotherapy can cause tumor cell apoptosis by inducing DNA damage, upregulating the p53 tumor suppressor gene, and through damage to the cellular lipid membrane. This in turn can lead to ceramide formation and activation of the stress-activated protein kinases/Jun amino-terminal kinases (SAPK/JNK) signaling pathway. The resultant damage-associated molecular patterns (apoptotic and necrotic cellular debris) can generate antigen-specific immunity through DC maturation and presentation of DC-processed antigen to T cells.[9]

Activation of the SAPK/JNK signaling pathway and the presence of damage-associated molecular patterns might also be partly responsible for other immunological effects seen after radiotherapy.[9] Studies in a variety of tumors have shown that radiation induces chemokines Chemokine (C-X-C motif) ligand, CXCL10, and CXCL16, which in turn promote recruitment of effector CD8 and T-helper 1 CD4 T cells.[10] Radiation has also been shown to induce a number of different proinflammatory cytokines, including interleukin (IL) 1β, TNF-α and type 1 and 2 interferons.[10] Additionally, in several cancer models, tumor cells exposed to radiation have been shown to have enhanced expression of major histocompatibility complex (MHC) class 1 molecules, costimulatory molecules, adhesion molecules (such as intercellular

Figure 1 **Radiation Effects on Immune Cells and Consequent Modulation by Radiotherapy.[9] Apoptosis Can Be Initiated by Radiation-Induced DNA Damage and Upregulation of the p53 Tumor Suppressor Gene, and by Damage to the Cellular Lipid Membrane, Which Can Induce Ceramide Formation and Activate the SAPK/JNK Signaling Pathway. SAPK/JNK Can Upregulate PKR Expression, Which in Turn Induces MHC and Cytokines via NF-κB. Radiation Treatment Induces Cellular Expression of MHC Class I, Adhesion Molecules, Co-Stimulatory Molecules, Heat Shock Proteins, Inflammatory Mediators, Immunomodulatory Cytokines, and Death Receptors**



Abbreviations: ATM = Ataxia Telangiectasia Mutated; CD = Cluster of Differentiation; DNA-PK = DNA-Dependent Protein Kinase; MHC = Major Histocompatibility Complex; NF-κB = Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells; PKR = Protein Kinase R; SAPK/JNK = Stress-Activated Protein Kinases/Jun Amino-Terminal Kinases.