Critical Reviews in Oncology/Hematology 112 (2017) 1–10

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Oncology reviews

Radiotherapy in the age of cancer immunology: Current concepts and future developments

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ARTICLE INFO

Article history:
Received 18 July 2016
Received in revised form
24 November 2016
Accepted 6 February 2017

Keywords:
Cancer
Radiotherapy

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http://dx.doi.org/10.1016/j.critrevonc.2017.02.002

ABSTRACT

Major advances in the knowledge of cancer biology and its interactions with tumor immune environment led to the emergence, in the last five years of new immunotherapy-based treatment strategies in cancer patients. At the same time, improvement in radiation technique and progress in radiobiology allowed in the last decade to expand the applications of radiotherapy in a growing number of settings. At present, there are strong theoretical basis to propose immune-enhanced radiation therapy that may represent in the future a new paradigm of treatment, combining the intrinsic power of radiotherapy to elicit a specific, systemic, tumor-directed immune response with modern highly conformal and precise dose delivery, in order to maximize response at the major site of disease and obtain durable disease control. The aim of

Immunotherapy
Radiobiology
Immune modulation

this review is to describe the principal mechanisms of immune modulation of response to radiation and investigational strategies to harness the potential of radiation-inducible immune response: radiation therapy is expected to be not just a local treatment but the cornerstone of a multimodal strategy that might achieve long-lasting tumor remission at the primary site and systemic efficacy metastatic lesions.

1. Introduction: biological basis of tumor-directed immune response

1.1. Overview

Cancer immunology is finally enjoying a late, though deserved, recognition by Academic Institutions all over the world: in 2013 it has been named "Breakthrough of the Year" by the editors of Science, while immune adaptation was admitted among the hallmarks of cancer since 2011 (Hanahan and Weinberg, 2011). Nevertheless, its way to the present glory has been paved by number of unsuccessful attempts to build a solid theoretical base starting from a bunch of sparse observations and anedoctical reports. Since pioneeristic observations by W. Coley in 1896 on spontaneous regression of malignancies after streptococcal infections and development of a "cancer vaccine" from bacterial extracts (Wiemann and Starnes, 1994), evidences of immune activations correlated to cancer multiplied during the past century, with development of therapeutic tools aiming at stimulating immune reaction toward tumour, in particular at the metastatic stage after failure of local treatments: as example, immunotherapy with interleukin-2 (IL-2) and Interferon 2 (IFN-2) has been for decades mainstays of systemic therapy for advanced kidney cancer and metastatic melanoma though appropriateness has been questioned due to limited efficacy, unspecific activity determining severe toxicity and to the development of targeted therapy drugs that made appear immune therapy an outdated strategy in the era of cancer biology and personalized medicine.

Curiously, radiotherapy, though universally recognized as a locoregional treatment, early showed an unexpected potential to enhance systemic response against cancer cells at distant sites of disease that was reported in 1953 by Mole who first coined the word "abscopal effect" (Mole, 1953) from the latin "ab," meaning "away from," and the Greek word "scopos," meaning "target".

Nevertheless in 60 years no efforts have been made, until recent times, to elucidate the links between biological effects of radiation and immune response, nor to harness the immune compartment as a therapeutic tool. Nowadays advances in immunotherapy of tumours with introduction of a novel class of agents like immune check-point inhibitors, technical progress in radiation delivery systems and renewed interest in baseline radiobiology research led in a few years to an impressive leap forward in understanding the basis of radiation-mediated immune activation.

In this review we will summarize the conceptual basis behind radioimmunology of tumors and review present and future applications to clinical management of patients.

1.2. From immunosurveillance to cancer immunoediting

Oncoimmunology has undergone a deep conceptual evolution in the last years passing from the simple, static view of immunosurveillance (detection and destruction of transformed cells by the immune system) formulated in 1957 by Burnett (Burnet, 1957) to a more dynamic, multi-staged concept named cancer immunoediting (Dunn et al., 2002) occuring in three sequential phases (Fig. 1):

a) Elimination, in which immune cells target cells undergoing malignant transformation in reason of aberrant antigen expression.
b) Equilibrium, in which the immune system exerts a selective pressure on surviving malignant cell, thus "shaping" their immunogenic profile with emergence of clones resistant to immune rejection
c) Escape, in which poorly immunogenic, "edited" tumor cells evade immune system control, leading to malignant progression (Vesely and Schreiber, 2013).

During the elimination phase, an initial cytotoxic macrophagic activation modulated by interferon gamma secreted by Natural Killers (NK) cells and γd lymphocytes, is stimulated by aspecific damage signalling pathways: tumor associated-antigens release ensues neoplastic cell lysis, that is followed by dendritic cell antigen uptake and processing that triggers CD4 T-lymphocyte mediated specific immunity (Schreiber et al., 2011). If elimination is incomplete or inadequate to raise a strong adaptative immune response, clone survival results in equilibrium state that finally leads to evasion from the host immune system control. Moreover, tumors are able to establish an immunosuppressive microenvironment that inhibits T-cell function both directly via expression of immunosuppressive molecules like surface FasL or TGF-β (Wrzesinski et al., 2007a), and undirectly by recruiting other cell populations like migratory tolerogenic dendritic cells, M2 macrophages, myeloid-derived suppressor cells (MDSCs) and regulatory CD4 T-lymphocytes (Treg), thus allowing further tumour progression (Lepique et al., 2009; Mougiakakos et al., 2010; Idoyaga et al., 2013).

Nevertheless immune confinement of disease could inhibit tumor growth and dissemination to a certain extent even at the evasion stage, driven by cancer genetic instability which generate new epitopes that stimulate a persisting, though poorly effective, adaptive immune activation. Finally, it has been reported that peritumoral lymphocytic infiltration is a predictor of outcome in different settings (Hiraoka et al., 2006; Galon et al., 2006; Pagès et al., 2010; Mahmoud et al., 2011).

In summary, immune reaction toward tumors is frequent but usually inadequate to achieve tumor rejection due to "editing" that wipes out strongly immunogenic antigens: efficient response could be evoked when multiple endogenous tumor antigens determine expansion of reactive T cells (antigen cascade), as is the case after radiation therapy (Hodge et al., 2012).

1.3. Effects of irradiations on immune response

It has been postulated that radiation therapy, as well as some antiblastic agents like oxaliplatin, could elicit the onset of a specific immune reactions toward cancer cell antigens through a mechanism named "immunogenic cell death" (ICD) (Kroemer et al., 2013). ICD might represent an alternative pathway of apoptosis triggered by ionizing radiation DNA damage showing peculiar features:

- Translocation at the cell surface of the cytosolic chaperon protein calreticulin that is recognized as a "find me signal", enhancing phagocytosis (Martins et al., 2011).