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Anti-Tumour Treatment

The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant

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ABSTRACT

Background: Recently, immunologic responses to localized irradiation are proposed as mediator of systemic effects after localized radiotherapy (called the abscopal effect). Here, we give an overview of both preclinical and clinical data about the abscopal effect in particular and link them with the immunogenic properties of radiotherapy.
Methods: We searched Medline and Embase with the search term "abscopal", "(non-targeted irradiation) OR (non-targeted radiotherapy)" and "distant bystander" from 1960 until July, 2014. Only papers that cover radiotherapy in an oncological setting were selected and only if no concurrent cytotoxic treatment was given. Targeted immune therapy was allowed.
Results: Twenty-three case reports, one retrospective study and 13 preclinical papers were selected. Eleven preclinical papers used a combination of immune modification and radiotherapy to achieve abscopal effects. Patient age range (28–83 years) and radiation dose (median total dose 32 Gy) varied. Fractionation size ranged from 1.2 Gy to 26 Gy. Time to documented abscopal response ranged between less than one and 24 months, with a median reported time of 5 months. Once an abscopal response was achieved, a median time of 13 months went by before disease progression occurred or the reported follow-up ended (range 3–39 months).
Conclusion: Preclinical data points heavily toward a strong synergy between radiotherapy and immune treatments. Recent case reports already illustrate that such a systemic effect of radiotherapy is possible when enhanced by targeted immune treatments. However, several issues concerning dosage, timing, patient selection and toxicity need to be resolved before the abscopal effect can become clinically relevant.

Introduction

Radiotherapy (RT) is highly effective anticancer treatment leading to local tumor control and potential cure for early stage cancer. Targeted ionizing irradiation has long been known to cause direct localized cell death. However, irradiation is also increasingly recognized to be able to induce tumor regression at non-irradiated, distant tumor sites. This phenomenon is called the "abscopal effect", a term first introduced by Mole in 1953 and later on broadened by Andrews to include distant normal tissue effects [1,2]. The existence of this type of effect is mainly described in sporadic case reports. Because documented abscopal regressions are rare, its clinical relevance is uncertain with current routinely used radiotherapy regimens. Nevertheless, recent insights regarding the immunogenic effects of RT and the biological mechanisms of the abscopal effect have provided renewed interest in the ability of radiotherapy to induce distant tumor regression leading to meaningful clinical benefit. The immune system has been proposed as the key component of abscopal effects after radiotherapy [3]. Local radiotherapy is known to induce an immunostimulatory form of cell death, called

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immunogenic cell death (ICD), leading to host immune responses [4–7]. The concept of ICD relies mainly on the release of damage associated molecular patterns (DAMPs) which trigger an antigen engulfment of dendritic cells (DC). This subsequently results in an improved antigen presentation to the cytotoxic immune system [8,9] (see Fig. 1). Irradiation is also known to alter the immune phenotype of the tumor by augmenting the presence of MHC I on the tumor cell surface, improving expression of cancer-testis antigens and upregulating the FAS/CD95 complex [10–13]. Furthermore, RT is recognized to create a cytokine pattern that facilitates migration and function of effector CD8+ T cells [14,15]. Therefore improved antigen expression and presentation as well as enhanced functioning of effector T cells provide a sound potential rationale for an immune mediated abscopal effect.

Here we overview the current state of knowledge of preclinical data and clinical experience regarding the abscopal effect. The aim of this review is to provide a systematic overview of the abscopal effect and identify links with the immunogenic properties of radiotherapy. Finally, we critically assess future therapeutic possibilities of radiotherapy in combination with the large number of emerging immunomodulatory agents [16].

Search strategy and selection criteria

References for this review were identified through searches of Medline and Embase with the broad search terms "abscopal", "(non-targeted irradiation) OR (non-targeted radiotherapy)" and "distant bystander" from 1960 until July, 2014. Titles and abstracts were screened by the main author and papers that were selected were verified by the other authors. English, Dutch and French clinical papers were included if they met the following criteria: patients had to receive single or multiple fractions of radiotherapy for any malignancy. Following radiotherapy, a non-irradiated tumor site needed to show size and/or metabolic regression. Biopsy confirmation of a responding distant site was not mandatory as clinical practice does not routinely require it. Papers were not considered eligible if whole body irradiation was used or if concurrent systemic treatment with a cytotoxic drug was given. Sequential cytotoxic treatment after radiotherapy was not allowed unless an abscopal radiotherapy response was assessed before the following systemic treatment was given. Concurrent or sequential immune modifying therapy was included though handled separately from radiotherapy-only cases.

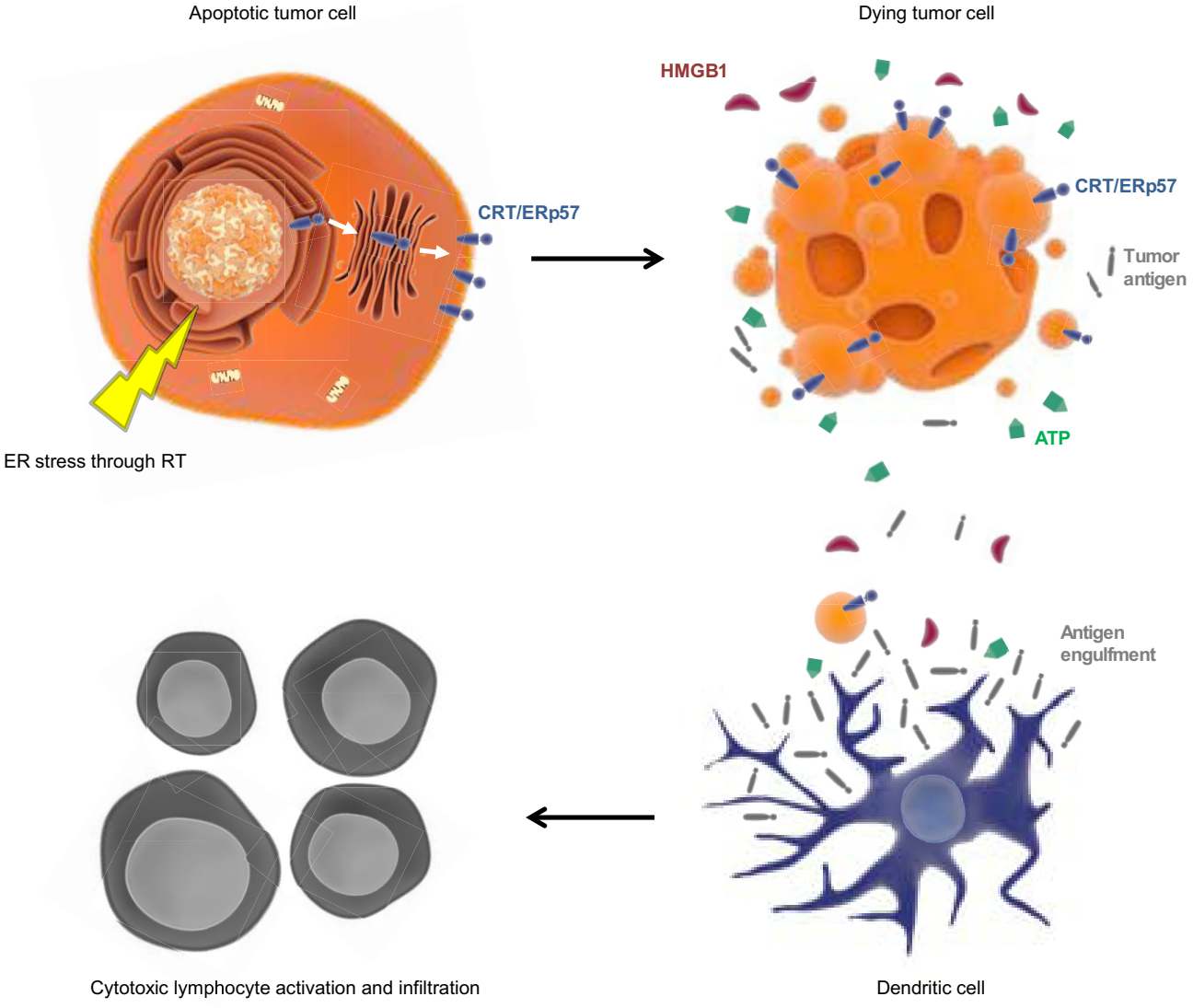

Fig. 1. Immunogenic cell death. Endoplasmatic reticulum stress induced by radiotherapy leads to apoptotic release of DAMPs such as ATP (find-me signal) and membrane blebs with the CRT/ERp57 complex (eat-me signal).