Chapter 13

BASIS OF CELL KILL FOLLOWING CLINICAL RADIOTHERAPY

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Abstract: Over one half of cancer patients are treated radiotherapy. Technological advances in radiation targeting and concurrent chemotherapy continue to improve clinical radiotherapy outcome. Modern radiotherapy clinical trials are ongoing with novel molecular-targeted agents, requiring an increased understanding of cell death signals in a tissue-specific manner. Herein, we critically appraise the relative roles of apoptosis, mitotic catastrophe and terminal growth arrest in relation to final clonogenic cell kill following radiotherapy. Mitotic catastrophe and terminal growth arrest form the basis of the majority of cell kill during radiotherapy for common epithelial tumors (e.g. prostate, breast, lung, etc.) whereas more sensitive tumors (e.g. lymphomas or germ cell tumors) undergo apoptosis. Targeting of apoptotic, cell cycle checkpoint and DNA repair pathways may further augment cell kill from all three death pathways. Using intra-treatment biopsies or non-invasive imaging may soon allow for prediction of individual patient response and judicious selection of molecular targeting based on specific tumor cell signaling.

Key words: radiobiology, apoptosis, mitotic catastrophe, cell cycle arrest, radiotherapy, clonogenic survival, survivin, p53, ceramide, senescence

7. INTRODUCTION

Since the discoveries by Roentgen and Curie more than a century ago, the biological effects of ionizing radiation have played a major role in diagnostic and therapeutic medicine. Radical radiotherapy, alone or in combination with chemotherapy, can be curative for a number of tumor sites.
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including tumors of the cervix, head and neck, prostate, bladder, lung, rectum, testes and lymphoma. Radiotherapy is delivered by interstitial brachytherapy implants or by external beam radiotherapy using linear accelerators (i.e., high energy x-rays and electron beams), $^{60}$Co sources ($\gamma$-rays produced by radioactive decay due to unstable nuclei) or charged particle accelerators. Improvements in radiotherapy outcome have been driven by sophisticated treatment planning methods allowing for improved physical targeting methods (e.g. conformal or intensity-modulated radiotherapy (IMRT)) and through increasing use of combined-modality therapy (i.e., radiotherapy concurrent with chemotherapy or hormone therapy). Future improvements in radiotherapy outcome will be the result of the judicious use of molecular biomarkers and genomic “fingerprinting”) to drive the selection of molecular-targeted drugs and improve local tumor control [1] and requires an increased understanding of cell death responses in a dose-, time- and tissue-specific manner.

The understanding of curative fractionated radiotherapy versus palliative radiotherapy is an important concept. Radiation dose is measured in grays (Gy) as the amount of energy absorbed per unit mass. Typical radiocurative regimens require a series of daily radiation dose fractions of 1.8 to 2 Gy over 6 to 8 weeks to achieve total doses in the order of 60 to 80 Gy. Higher dose per fractions can be used in palliative settings (e.g. 8 Gy single dose or 5 to 10 fractions of 3 to 5 Gy) to relieve symptoms resulting from compression of surrounding tissues. Curative fractionated regimens attempt to maximize the therapeutic ratio in which a maximum dose is delivered to the tumor in an effort to sterilize all stem cells (clonogens) capable of tumor regrowth, but is a dose that is tolerable dose to the normal tissues within the irradiation volume. The final level of cell killing during a period of fractionated radiotherapy is related to multiple factors termed the 5 R’s of radiotherapy: the intrinsic radiosensitivity of the normal and tumor cells; the redistribution of cells within the cell cycle between treatments; the reoxygenation of hypoxic cells during the course of radiotherapy; the repopulation of normal and tumor cells during radiotherapy; the repair of normal tissues between each radiotherapy fraction [2].

Many studies have solely used large single radiation doses (e.g. 10 to 20 Gy) to assess cell death responses following irradiation. This may activate different signaling and cell death pathways from other experiments using more clinically-relevant doses of 2 Gy which are used during radiocurative fractionated protocols. The sole use of high doses of radiation to study cell death mechanisms may explain some of the difficulties in extrapolating cell biological data in vitro to the clinical outcome of patients in vivo.

This review will first provide a general background regarding the cellular response to ionizing radiation in relation to intracellular damage sensing and