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Integrating chemoradiation and molecularly targeted therapy☆

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ABSTRACT

While the advent of combined chemoradiation has improved outcomes for innumerable patients with locally advanced cancers, further improvements are urgently needed. Escalation of either chemotherapy or radiotherapy is associated with unacceptable toxicity. An alternative strategy is the integration of chemoradiation and molecularly targeted therapies, which exploits biological differences between cancer and normal tissue and should therefore increase efficacy while maintaining tolerable toxicity. Combining chemoradiation with agents that modulate tumor-specific pathways such as cell cycle checkpoints, PARP signaling, EGFR signaling, the PI3K/AKT/mTOR axis and androgen signaling has shown immense promise in preclinical and clinical studies, as have combinations with environmentally-targeted agents against the immune system and angiogenesis. The optimal application of these strategies will likely require consideration of molecular heterogeneity between patients and within individual tumors.

Contents

1. Overview

Radiation therapy has been in use for more than a century and, with surgery, forms the basis for local oncologic management. Radiation has helped cure many cancers; however its use in isolation has limitations that cannot be overcome by simple dose escalation. Over the past several decades, two main strategies have been utilized to improve the efficacy of radiation therapy. The first involves administering chemotherapy concurrently with radiation (here termed chemoradiation). This approach sensitizes cancer cells to radiation and improves outcomes in

Abbreviations: SBRT, Stereotactic body radiation therapy; 5-FU, 5-fluorouracil; FdUMP, Fluoro-deoxyuridine-monophosphate; FdUTP, Fluoro-deoxyuridine-triphosphate; FUTP, Fluorouridine triphosphate; CHK1, Checkpoint kinase 1; PARP, Poly(ADP-ribose) polymerase; EGFR, Epidermal growth factor receptor.

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numerous malignancies. The second, stereotactic body radiation therapy (SBRT), has been facilitated by technological advances that allow the delivery of ablative doses of radiation to small well circumscribed lesions resulting in high rates of long lasting local control [1,2]. Dose-escalated SBRT is not optimal for locally advanced tumors with significant microscopic spread or involved lymph nodes due to the high dose of radiation that would be delivered to surrounding normal tissues and resultant toxicity. In such situations, chemoradiation is preferred. The advent of highly conformal radiation allowed its combination with full dose chemotherapy [3] but further intensification of either the chemotherapy or the radiation aspects of chemoradiation has resulted in unacceptable toxicity. As such, there have recently been increased efforts to combine chemoradiation with molecularly targeted therapies, which exploit biological differences between cancer and normal tissue and should therefore have increased efficacy that outpaces additional toxicity. In this review, we discuss the historical context of chemoradiation and recent progress in integrating cancer- and environment-directed molecularly targeted therapies with chemoradiation. With regard to cancer-specific pathways, we focus on those that mediate cell cycle arrest and DNA damage repair as well as pro-survival pathways upregulated by chemoradiation. We also cover emerging clinical strategies to alter environmental pathways including angiogenesis and immune checkpoints, both of which have potential to increase chemoradiation efficacy.

2. Chemoradiation

Among the first chemotherapeutics used in chemoradiation were the anti-metabolites, which structurally mimic the precursors to nucleic acids (i.e., nucleobases or nucleosides) [4]. The antimetabolite radiosensitizers currently in clinical use include gemcitabine, 5-fluorouracil (5-FU) and the 5-FU prodrug capecitabine. Intracellularly, 5-FU is converted into its active metabolites fluoro-deoxyuridine-monophosphate (FdUMP), which exerts cytotoxicity by inhibiting thymidylate synthase (TS), as well as fluoro-deoxyuridine-triphosphate (FdUTP) and fluorouridine triphosphate (FUTP), which contribute to cytotoxicity by misincorporating into DNA and RNA respectively. Gemcitabine achieves its cytotoxicity via its downstream metabolites dFdCDP, which inhibits ribonucleotide reductase and depletes nucleotides (especially dATP), and dFdCTP, which competes with dCTP for incorporation into DNA [5]. In contrast to their cytotoxic activity, the radiosensitizing properties of the antimetabolites appear to be related to their DNA-directed effects including their ability to deplete nucleotide pools and redistribute cells into S-phase, where the combination of ionizing radiation and antimetabolite leads to complex and slowly repaired DNA damage [6,7]. In the clinic, antimetabolites are typically combined with radiation therapy for gastrointestinal tumors and have improved locoregional control and survival in numerous malignancies including rectal [8], gastric [9], pancreatic [10] esophageal [11] and anal cancers [12].

The second main class of chemotherapeutics used in chemoradiation is direct DNA modifying agents, which include platinum based agents and temozolomide. Cisplatin and related compounds induce cytotoxicity by directly forming DNA cross-links that interfere with DNA replication leading to double strand DNA breaks and cell death. By contrast, temozolomide directly alkylates DNA and forms methyl adducts primarily at the O^6 position of guanine [6]. These methyl adducts are often repaired improperly leading to double strand DNA breaks and cell death. Radiation-induced double strand breaks near cisplatin–DNA adducts or temozolomide-induced methyl adducts are complex and are repaired with slow kinetics, which may account for the ability of these agents to radiosensitize [6]. The combination of platinum-based chemotherapy and radiation improves survival and local control in the treatment of locally advanced lung [13], head and neck [14], esophageal [15], cervical [16] and vulvar cancers [17]. Temozolomide is combined with radiation as the standard treatment for glioblastoma, where it improves local control and overall survival [18].

3. Combining chemoradiation with cancer-directed molecularly targeted agents

While combining chemotherapy and radiation has improved outcomes in numerous malignancies, improvements are still needed, especially in glioblastoma and pancreatic cancer, which remain fatal for most patients. Escalating the dose of radiation given with concurrent chemotherapy is a promising approach, but has been associated with excessive toxicity in some cases [19,20]. Similarly, intensifying the chemotherapy regimen used with radiation is frequently limited by toxicity [21,22]. Given these limitations, there is increasing interest in combining chemoradiation with molecularly targeted agents (Fig. 1). By using agents that target molecular pathways that are related to the chemoradiation response and are relatively tumor-specific, these combinations are a promising strategy to augment the efficacy of chemoradiation without prohibitive toxicity.

3.1. Cell cycle checkpoint inhibitors

In response to genotoxic stress such as chemoradiation, cells typically arrest at one of a variety of cell cycle checkpoints to repair DNA damage prior to completing mitosis (Fig. 2). Because unrepaired double strand breaks typically mediate tumor cell killing, one strategy to increase the efficacy of genotoxic treatments such as chemoradiation is to prevent checkpoint arrest. The two best-studied cell cycle checkpoint inhibitors are checkpoint kinase 1 (CHK1) and the related kinase WEE1.

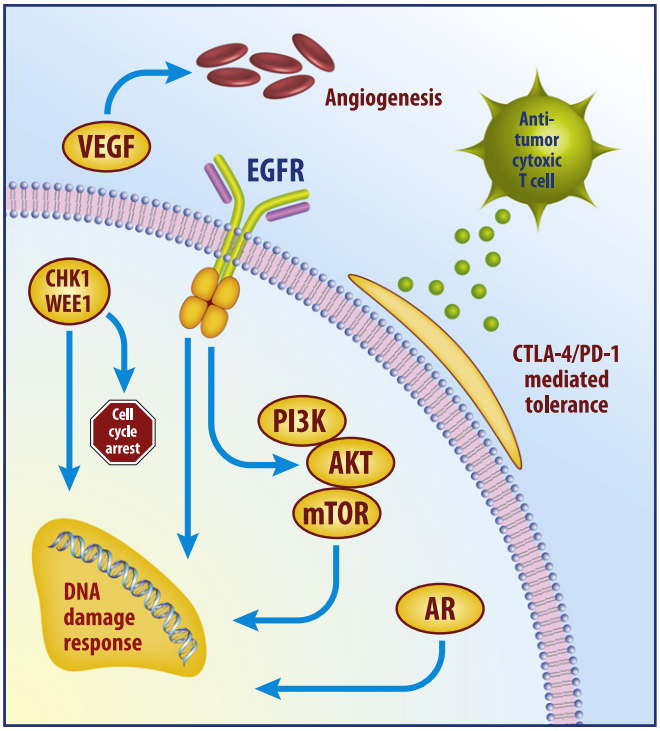

Fig. 1. Promising targets for combining chemoradiation and molecularly targeted therapies. Promising pathways for combination with chemoradiation are depicted in orange. Chemoradiation robustly induces the DNA damage response and cell cycle arrest. Inhibition of these pathways either via CHK1/WEE1 inhibition or other targets can lead to sensitization. Chemoradiation also activates EGFR and PI3K/AKT/mTOR signaling, which can be inhibited thereby increasing efficacy. In prostate cancer, AR signaling can stimulate the DNA damage response and its inhibition may potentiate chemoradiation efficacy. Chemoradiation can increase the presentation of cancer-specific neoantigens and blocking PD-1/CTLA-4 immune checkpoints may improve the immune response to these neoantigens. VEGF secreted by tumors can stimulant aberrant vascularization and paradoxically increase hypoxia. Normalization of this vasculature may increase the efficacy of chemoradiation.