Published in final edited form as:

Cancer J. 2019 ; 25(2): 106–115. doi:10.1097/PPO.0000000000000369.

Repurposing Drugs for Cancer Radiotherapy: Early successes and emerging opportunities

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Abstract

It has long been recognized that combining radiotherapy with cytotoxic drugs such as cisplatin can improve efficacy. However, while concurrent chemo-radiotherapy improves patient outcomes, it comes at costs of increased toxicity. A tremendous opportunity remains to investigate drug combinations in the clinical setting that might increase the benefits of radiation without additional toxicity. This chapter highlights opportunities to apply repurposing of drugs along with a mechanistic understanding of radiation effects on cancer and normal tissue to discover new therapy-modifying drugs, and help rapidly translate them to the clinic. We survey candidate radiosensitizers that alter DNA repair, decrease hypoxia, block tumor survival signaling, modify tumor metabolism, block growth factor signaling, slow tumor invasiveness, impair angiogenesis, or stimulate anti-tumor immunity. Promising agents include such widely used drugs as aspirin, metformin and statins, offering the potential to improve outcomes, decrease radiation doses and lower costs. Many other candidate drugs are also discussed.

Keywords

Repurposing; Radiotherapy; Drugs; Radiosensitizer; Immunotherapy; DNA repair; Countermeasures

Introduction

Radiotherapy is one of the most cost-effective options for the treatment of cancer, and more than half of all patients will receive radiotherapy at some point during their cancer treatment¹. Radiotherapy can be used as a single modality, or combined with other treatments in a multi-disciplinary fashion. Forty percent of cancers may be cured by radiotherapy alone, or when combined with other cancer therapies². In recent decades, thousands of preclinical studies and clinical trials have examined concurrent treatment with radiotherapy and cytotoxic, targeted or monoclonal cancer drugs, yielding several promising combinations^{3–5}. Chemotherapy agents including temozolamide, cisplatin, 5-FU, cetuximab, and mitomycin C have each been approved by the Food and Drug Administration (FDA) for

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concomitant use with radiotherapy for specific indications. However, many other drugs that are FDA approved for other indications, including many unrelated to cancer, and/or are in the pipeline, have the potential to improve radiotherapy. The purpose of this chapter is to highlight opportunities to take advantage of our knowledge of mechanisms of radiation effects on tissue and tumor cells to repurpose existing drugs as radiosensitizers and/or limit radiation toxicity. In particular, given the potential of external beam radiotherapy to address the impending cancer crisis in developing countries⁶ and the potential to repurpose off-patent drugs as sensitizers, this strategy may provide a uniquely cost-effective means to improve cancer outcomes globally.

Although the primary effect of ionizing radiation is considered to be genomic damage and particularly the formation of chromosomal DNA double strand breaks (DSBs), multiple features of the tumor and host factors determine whether a radiation dose will be sufficient, creating a wide range of potential targets by which repurposed drugs might modulate radiation effects. Thus, in addition to agents that affect DNA repair, drugs targeting hypoxia/perfusion, metabolism, immunogenicity, proliferation, angiogenesis, survival signaling and invasion/metastasis among others all have the potential to enhance the radiotherapy response. Here, we provide some of the emerging biological rationale and describe relevant preclinical and clinical data behind some of the most promising radiotherapy/drug combinations. Unlike most cancer repurposing efforts, the agents need not offer the patient some benefit on their own. Here, the ultimate goal is simply to increase the therapeutic index of radiotherapy, enhancing tumor control without increasing toxicity to surrounding normal tissues.

Repurposing to target DNA repair after radiation

Most chromosomal damage induced by ionizing radiation, whether delivered as photons, electrons, protons or other particles, is indirect, resulting from hydroxyl radicals attacking the nucleotide bases and backbone. When cells are exposed to so-called high linear energy transfer (LET) radiation such as accelerated particles (e.g. 400 MeV carbon ions), the dense track of hydroxyl radicals, electrons and direct DNA ionizations is sufficient to induce instantaneous DSBs. However, most radiotherapy is performed with X irradiation in the ~6 MeV energy range where hydroxyl radicals are too scattered to cleave both DNA strands directly. The accumulation of chemical damage from multiple events over time leads to direct and repair-dependent DSBs. When a diploid cell is exposed to 1 Gray of X-irradiation (absorption of 1 J/kg), a typical clinical dose, it may be subjected to 100,000 ionization events resulting in 1000 single strand DNA breaks (SSBs) and 25–40 DSBs⁷. If the SSBs are not repaired, the DNA is replicated and/or DSBs persist through mitosis, the resulting mitotic catastrophe may be sufficient to prevent further proliferation. As such, there has long been considerable interest in repurposing cancer therapeutics and other drugs to target DNA repair and other elements of the DNA damage response after irradiation.^{3,8–10}

Not surprisingly, many cytotoxic agents display compound effects when combined with radiation, leading to the concept of concurrent chemoradiotherapy.⁵ Among the first agents considered as radiosensitizers were nucleoside analogs¹¹, following on discovery of potentiation of radiation by the thymidylate synthase inhibitor and ribonucleotide precursor

5-fluorouracil (5-FU). The antifolate pemetrexed and ribonucleotide reductase inhibitor hydroxyurea have related effects on nucleotide pools. By contrast, halogenated pyrimidine analogs including bromodeoxyuridine (BrdU) and gemcitabine are incorporated into DNA to mediate their radiation-enhancing effects, potentially by increasing DSBs. In general, the antimetabolites can delay repair of radiation damage at doses that are not markedly toxic on their own.

Following on the success of 5-FU in improving the anti-tumor effects of radiotherapy, nearly all cancer drugs approved as monotherapies over the last five decades have also been examined in combination with radiation, leading to several effective regimens. Among chemotherapy drugs that have been most successfully repurposed for concurrent chemo-radiotherapy are alkylating agents, including mitomycin C, platinum-containing drugs such as cisplatin and carboplatin, and temozolomide⁵. Topoisomerase poisons such as topotecan have also been examined as radiation sensitizers.¹² The rationale for increasing DNA overall damage to enhance radiation is not straightforward. The immediate benefits of alkylating agents in the radiation field may only be additive¹³, but other effects such as altering tumor cell recovery and suppressing distant micrometastases may contribute to overall superiority of chemo-radiation over radiation alone in many diseases. In turn, chemo-radiotherapy with alkylating agents is associated with increased normal tissue toxicity that can offset the benefits.

Given the toxicity of most cancer drugs, there has been considerable interest in identifying “true” radiosensitizers that potentiate radiation without incurring genotoxic effects on their own. Studies of DNA damage response pathways and DSB repair mechanisms have led to the discovery of diverse small-molecule inhibitors that block critical targets and nearly all of these agents have been combined with radiation *in vitro* and in preclinical models to assess potential as radiation modifiers. The related PIKK enzymes ATM, ATR and DNA-PK have overlapping roles in the initial DNA damage recognition steps in the DNA damage response.¹⁴ Small-molecule kinase inhibitors targeting one or more of these enzymes have largely failed on their own as cancer drugs, but remain under evaluation in combination with genotoxic agents including radiotherapy. Similarly, inhibitors identified to target downstream effectors such as the nuclease Mre11 have been examined as radiation sensitizers *in vitro* and in preclinical studies. An alternative strategy is to target enzymes responsible for critical steps in DSB repair. *In vitro* studies have revealed novel inhibitors of “ideal” radiosensitization targets such as the recombinase Rad51¹⁵ or DNA ligases¹⁶, raising the potential to apply repurposing to accelerate translation to the clinic.

Given the role of chromatin in both limiting the effects of radiation on DNA and then the detection and repair of radiation damage, a wide range of drugs targeting epigenetic modifiers have also been examined as radiosensitizers. While the nucleoside analog DNA methyltransferase (DNMT) inhibitors zebularine, 5-azacytidine and decitabine have been shown to radiosensitize *in vitro*, with limited data in tumor models, firm links to DNA repair remain to be established.¹⁷ Poly(ADP-ribose) polymerases (PARP) are among the first proteins to bind at DNA damage sites, incorporating NAD⁺ to modify histones and other proteins with poly(ADP-ribose) (PAR), leading to chromatin relaxation and recruitment and activation of DNA repair proteins. Multiple PARP inhibitors have advanced to the clinic and

are now under active investigation in multiple clinical trials in combination with radiotherapy¹⁸. Agents such as the approved drug olaparib display high PARP trapping activity, leading to protein adducts and DNA damage, much like a topoisomerase inhibitor. PARP inhibitors such as veliparib that are less prone to trap PARP may display less activity on their own but are promising for repositioning as radiosensitizers. Other steps in DNA damage recognition have also been targeted. Initial work with the histone deacetylase (HDAC) inhibitor valproic acid¹⁹ established the potential for radiosensitization of this class of enzymes.²⁰ Subsequent studies have demonstrated radiation modifying effects of agents targeting multiple HDACs, histone acetyltransferases (HATs), histone methyltransferases (HMTs) such as EZH2²¹ and G9A²², histone demethylases (HDMs) such as UTX²³, histone ubiquitylation enzymes such as BMI1²⁴ and diverse other enzymes that regulate chromatin protein modification, stability and protein-protein interactions. Targeting chromatin readers that recognize epigenetic marks, as demonstrated by the BET family bromodomain inhibitors²⁵, also has considerable potential. Given the key roles for chromatin in DNA damage response, the continuing development of new epigenetic drugs and their comparatively low toxicity, these agents appear to represent a promising source of candidates to consider for repurposing as radiosensitizers.

Overall, the lack of approved agents that target known DNA repair proteins has limited repurposing efforts. In turn, a critical limitation has been that established assays to directly detect DNA damage and repair are generally unsatisfactory for small molecule screening. For example, the alkaline and neutral comet assays (single cell gel electrophoresis) are well-validated tests for SSBs and DSBs respectively, but may be better suited to secondary analysis rather than primary screening. Recent efforts to adapt the comet assay to a multiwell format as in the CometChip may allow sufficient throughput for repurposing screens for radiation sensitizers.^{26,27} Lacking facile methods to directly track DNA repair, diverse strategies based on DNA damage reporters and proxies have been pursued. In particular, fluorescent and luciferase reporters of DNA damage signaling or DNA repair can provide simple primary assays for multiwell screens. Repurposing screens using fluorescent reporters have identified diverse agents as candidate DNA repair inhibitors.^{28–31} A common strategy has been to detect DSBs by the characteristic modifications of the adjacent chromatin, including the phosphorylation of histone H2AX³², an early indicator of activation of ATM, ATR and/or DNA-PK. Phosphospecific antibodies can detect the resulting foci of γ H2AX immunoreactivity. Other proteins that colocalize with γ H2AX can also be detected, including the DNA repair protein 53BP1,³³ which can be tracked by following relocation of GFP fusions in live cells. GFP reporters that change expression or color depending on DSB repair allow direct assay for inhibitors that affect specific DNA repair pathways^{29,30}). Among promising agents identified in screens and validated in preclinical models^{34,35} have been antibiotics, anti-psychotics, anti-depressants, statins, and a wide range of other widely used drugs with attractive toxicity profiles. Incidental use of these commonly used prescription drugs is common in patients undergoing radiotherapy due to intercurrent disease, providing the opportunity to examine influences on outcomes such as local control and progression-free survival by mining medical records.³⁶

Repurposing to leverage radiation effects beyond DNA damage

Although it has long been taught that the therapeutic benefit of radiotherapy is mediated by direct cancer cell killing via inducing potentially lethal damage in the form of chromosomal DSBs, this dogma relies on surprisingly limited evidence.^{37–39} Indeed, along with DSBs, the potentially hundreds of thousands of ionization events induced in each cancer cell by a therapeutic X-ray dose can produce a wide range of other effects that are commonly described as “oxidative damage”. Significant impacts can be observed on organelles including mitochondria, other macromolecules such as proteins and lipids, redox regulators such as glutathione, and metabolic intermediates including the deoxyribonucleotide pool. Thus, independent of DNA repair, survival also requires adaptive mediators such as glutathione antioxidant activity,^{40,41} chaperones,⁴² ER stress response and autophagy,⁴³ the Nrf2-Keap1 antioxidant response,⁴⁴ and mitochondrial metabolism⁴⁵ providing additional opportunities for repurposing. Further, radiation can induce persistent oxidative stress, potentially mediated by activation of NADPH oxidases,^{46,47} amplifying not only the DNA damage but also the other cellular effects. The many (!) drugs and natural products that induce reactive oxygen via redox cycling and other mechanisms provide further opportunities for radiation sensitizers, though a caveat is that, like many commonly used chemotherapy agents, these drugs are likely to display dose-limiting toxicities.

Repurposing to decrease tumor hypoxia

Hypoxia has long been known to dramatically reduce the effectiveness of radiotherapy, leading to a two-to three-fold reduction in biological effectiveness. This is typically ascribed to an important role for oxygen interactions with radicals or other transient species and stabilizing otherwise reversible or repairable damage. Tumor hypoxia may have multiple origins, but a key contributor is likely the disordered vasculature characteristic of tumors. The inadequate perfusion of tumors leads to a patchwork of watershed regions and domains of chronic or intermittent hypoxia, so that radiation doses that may be effective on oxygenated regions may have only minimal benefit overall. Along with conventional drug discovery efforts, drug repurposing has been examined as a strategy to restore oxygenation to tumor tissue via suppressing oxygen utilization or increasing perfusion.^{48–52}

Targeting Tumor Metabolism-Statins, Aspirin, and Metformin

Statins

Statins have been widely used for the treatment of hyperlipidemia, and have been shown to possess anti-tumor effects, partly attributed to their ability to interfere with metabolic pathways essential for the survival of cancer cells⁵³. In one preclinical study, pre-treatment of head and neck squamous cell carcinoma with 2 weeks of simvastatin prior to injection of tumors in mice increased overall survival (OS).⁵⁴ The increase in OS was likely related to increased expression of monocarboxylate transporter 1 (MCT 1), which leads to a reduction in tumor lactate content. The MCT transmembrane proteins (MCT 1 and MCT 4) control lactate metabolism and have been associated with poor prognosis in solid tumors, such as colorectal cancer⁵⁵. Modulation of the MCT 1 pathway, via the use of statins has the potential to serve as radiosensitizer in the future^{56,57}. The previous preclinical findings of

statins, possibly improving patient outcomes, have also been validated in at least three retrospective clinical outcome studies. One retrospective study of 519 inflammatory breast cancer patients treated with post mastectomy radiotherapy, demonstrated that of the 53 patients that used statins during radiotherapy had a higher local recurrence free survival compared with non-statin users⁵⁶. Another retrospective study of 691 prostate cancer patients, of which 189 used statins during radiotherapy, also found improved biochemical failure rates and relapse free survival compared with non-statin counter parts³⁶. 358 non-metastatic rectal cancer patients who underwent neo-adjuvant chemoradiation, and were also on concomitant statins, also saw improvements in pathological complete response rates (pCR)⁵⁸. One phase I/II has demonstrated that high doses of lovastatin can be given safely with radiotherapy, in 18 anaplastic and/or glioblastoma patients. The impact of local control, progression free survival, and OS is not known with use of the statins and radiotherapy. Further testing in future clinical trials are needed.

Aspirin

Aspirin inhibits the COX enzyme by acetylation of serine 530 (COX-1) and serine 516 (COX-2). Thus, arachidonic acid is not metabolized, and leads to blocking of prostaglandin formation, and potentially improved tumor control⁵⁹, through the p53 protein pathway⁶⁰. COX-2 overexpression has been shown to be associated with increased cell proliferation, cellular senescence and chemoresistance in nasopharyngeal carcinoma (NPC) cell lines, likely mediated through the p53 pathway⁶¹. Knockout of COX-2 on the other hand, reduced cell proliferation, promoted cellular senescence and overcame chemoresistance in NPC cell lines. Radiation with concomitant aspirin use has also been shown to induce a synergistic reduction in cell survival of A549 and H1299 lung cancer cell lines, compared with normal human lung fibroblasts (NHLFs). The level of apoptosis was increased in the cancer cell lines, and that this was thought to be due to the translation of the p6 locus, which lead to induction of apoptosis and increased sensitive to radiation.⁶²

Several COX inhibitors have been shown to revert immune suppression caused by radiotherapy for breast cancer⁶³, and aspirin (600 mg) given before radiation and twice daily for 1 week after radiation, has been shown to reduce esophagitis in opossums⁶⁴, as well as lead to improvements in epithelial ulceration⁶⁵ and radiation enteritis.⁶⁵ Thus, aspirin as well as COX1/COX2 inhibitors, may have the potential to improve radiotherapy index by improving tumor control and reduce potential toxicity by mediating post radiotherapy inflammation.⁶⁶ To date, there is one randomized trial⁶⁷ that tested cosmetic outcome after breast conservative surgery for early stage breast cancer. This trial, did not find any benefit on acute (erythema, edema, discomfort) or late effects (induration, telangiectasia). Further trials are needed to test if COX1/COX 2 inhibitors and/or aspirin may improve outcome for radiotherapy cancer patients. Zaorsky et al.⁶⁸ provides the largest retrospective series investigating the use of aspirin and stains on prostate cancer patients undergoing radiotherapy. The authors⁶⁸ found that prostate cancer patients on aspirin or statin had much lower risk of early biochemical failure. The risk of non-use of aspirin had an odds ratio of 2.05, and the use of non-statins was 2.47. Both findings were statistically significant, amongst the 2051 patients treated between 1981 and 2006 with a median definitive radiation dose of 76 Gy. Other preclinical⁶⁹ and clinical studies⁷⁰ have suggested that that aspirin may

benefit the radiotherapy therapeutic index, which may translate to improved overall survival⁷⁰ in high-risk prostate cancer patients treated with radiotherapy. Aspirin use during preoperative chemoradiation in colorectal cancer patients may also increase tumor downstaging (67.6 % vs 43.6%, $p=-.01$), higher progression free survival (86.6% vs 67.1%) and overall survival (90.6% vs 73.2%), as noted in a retrospective study of 241 patients.⁷¹ To the contrary, Hardie *et al.* did not find any improvements in toxicity or pathological complete response with statin or aspirin use in rectal cancer patients, and suggested that prospective randomized trials are needed to further test the benefits of statins and aspirin in cancer patients^{53, 72}. There may also be racial differences among radiotherapy patients, who may or may not benefit with concomitant use of aspirin during radiotherapy. One study found that African American patients undergoing radiotherapy who also used aspirin had improved biochemical outcomes and reduced distant metastases.⁷³

Metformin

Diabetes patients have been shown to be at increased risk for colon cancer⁷⁴. In a large, population based study of 493,704 men and 502,139 women, metformin use significantly lowered the risk of colon cancer by 27%. The duration of metformin use showed an inverse trend compared with non-users, and the authors concluded that metformin may protect against colon cancer⁷⁴. Another retrospective study of type II diabetes mellitus patients suggested a 30% improvement in OS with the use of metformin vs use of other diabetic agents⁷⁵. The association of metformin use, reducing risk of all cancers has been observed in one meta-analysis,⁷⁶ and one prospective study demonstrated that it may also reduce colonic epithelial proliferation and rectal aberrant crypt foci formation.⁷⁷

Metformin may also enhance tumor radio sensitivity *in vitro* and *in vivo*. A systematic review of 17 cohort studies involving radiotherapy patients, demonstrated that tumor responses was higher in patients who were treated with metformin vs. those who were not.⁷⁸ Furthermore, the 2 year and 5 yr OS was also superior in those diabetes patients treated with metformin vs. those that were not.⁷⁸ One preclinical study suggested that metformin can preferentially radiosensitize luminal breast cancer cells by altering the intracellular reactive oxygen species (ROS) levels via modulation of the Trx family of proteins⁷⁹. Metformin may also improve tumor oxygenation and response to radiotherapy in tumor xenograft models via inhibition of mitochondrial complex 1.⁵² The authors suggested that metformin may represent an effective and inexpensive way to improve outcomes for radiotherapy patients.⁵² One retrospective study of breast cancer patients treated with radiotherapy while also concomitantly on metformin, suggested increased acute loco-regional toxicity compared with alternative diabetes medications.⁸⁰ In hepatocellular carcinoma patients, there may be an improvement in OS in patients that were treated with stereotactic radiosurgery, while also on metformin.⁸¹ Further trials are needed to validate the role that metformin may play in potentially improving the outcome for radiotherapy patients.

Enhancing apoptosis, mitotic catastrophe and senescence after radiation

Even at the time of the seminal observations that led to the conclusion that chromosomal DNA served as the critical target of radiation in cancer and normal cells^{37,38}, it was already

recognized that loss of clonogenicity was not necessarily linked to loss of cell viability, *per se*. While apoptosis is an important early response to radiation in critical normal tissues such as bone marrow and intestinal mucosa, the high apoptotic threshold in many cancer cells may allow lethally damaged cells to persist indefinitely. Lethally irradiated cancer cells may directly undergo proliferative arrest or undergo mitotic catastrophe by completing one or more cell cycles, with or without undergoing cell division, leading to large, multinucleate cells and/or microcolonies. Marcus described formation of “giant cells” after irradiation of HeLa cells in 1956 as characteristic outcome of radiation^{37,82}. While the term giant cell has fallen out of favor, this form of division arrest is now considered a form of accelerated cellular senescence^{83,84}. Based on seminal studies in yeast⁸⁵, cancer cell microcolonies may similarly represent continued division despite aneuploidy, resulting in eventual arrest or cell death upon depletion of critical components. Repurposing to discover pro-senescent radiosensitizers has been successful using screening to detect persistent DNA damage after irradiation,³⁴ but this may unnecessarily limit discovery. With this in mind, the many successful repurposing screens that have been pursued to detect enhance loss of clonogenicity, increased apoptosis, or enhanced senescence after irradiation, using phenotypic assays of cell, spheroid or tumor survival and proliferation^{86–91}, provide evidence of feasibility for taking similar approaches to discovering novel radiosensitizers that specifically target cell cycle without affecting DNA damage responses.

Targeting Tumor Growth and survival.

Although tumor initiation may be instigated by oncogenic mutations, it is regulated and propagated by growth factors in the subsequent steps of tumor progression, leading to tumor growth and invasion⁹². Growth factors are small polypeptides that bind to cell surface receptors to activate intracellular kinase domains^{92,93}. These may then stimulate multiple, but specific intracellular signals such as mitogen-activated protein kinase (MAPK), the phosphatidylinositol 3-kinase (PI3K) or transcription factors such as signal transducer and activator of transcription, STATs and SMADs^{94,95}. Some of these distinctive growth factors include: Epidermal growth factor (EGF), platelet derived endothelial growth factor (PDGF), fibroblast growth factor (FGF), TGF- β and many others. Due to their importance in tumor progression, these growth factors have been the target of cancer therapies for decades now⁹⁶. These molecularly targeted therapies have found their own niche along with the classical therapies such as chemo- and radiotherapy⁹⁷. Most drugs were primarily designed to block cancer cell growth by inhibiting the growth factor signaling at various steps, such as, by lowering the levels of growth factor in the body, by blocking the growth factor receptor on the cancer cell so that growth factor is unable to bind, and by blocking the signals inside the cell once the growth factor binds to the receptor⁹². These different drugs can be categorized into groups depending upon the step they block in the signaling pathway. They can be monoclonal antibodies that bind to growth receptor or ligand, and thus block the receptor-ligand interactions [Anti-receptor monoclonal antibodies cetuximab, panitumumab (anti-EGFR)^{98,99}; trastuzumab, pertuzumab (anti-HER2)^{100,101}], or they can act as tyrosine kinases inhibitors (TKIs) and block the downstream signaling [erlotinib, gefitinib, lapatinib, imatinib, sunitinib, sorafenib¹⁰²]. Further, other drugs were developed that act as inhibitors of downstream MAPK or PI3K pathways [SF1126, GDC0941 (PI3K inhibitors)^{103,104};

sorafenib (RAF inhibitor)¹⁰⁵; AZD6244, CI-1040 (MEK inhibitor)^{106,107}. Although, these drugs show promise due to their minor adverse effects, responses to these drugs are often low to moderate⁹². Combining these drugs with chemo- or radiation therapy should enhance the efficacy of these drugs, and help reduce the dose of chemotherapeutic agents or radiation to minimize off target toxicity.

Another major goal of cancer therapies is to promote the death of cancer cells, leaving the normal cells unharmed. Inducing apoptosis in cancer cells may specifically target the rapidly dividing cells with less direct toxicity to the host. But on the downside, resistance to apoptosis by cancer cells may explain why these apoptosis directed therapies sometime fail. In order to reduce the resistance to these drugs, combination radiation therapy may increase sensitivity to these drugs, thus reducing the resistance by cancer cells. Some of the agents that induce apoptosis are: (a) radiotherapy (depending on the dose) and majority of chemotherapies induce apoptosis of cancer cells in both *in vitro* and *in vivo* systems^{108,109}. (b) death-receptor ligands, such as Tumor necrosis factor (TNF)¹¹⁰. Although, not widely used as an anti-apoptotic drug, it can indirectly induce apoptosis of cancer cells by affecting endothelial cells, and may show benefit in combination with radiation and chemotherapeutic drugs, since it indirectly target cancer cells by modulating cells that aid cancers. (c) B-cell lymphoma-2 (BCL-2) antagonists. High levels of anti-apoptotic BCL-2 family proteins are thought to be responsible for cancer growth in many cancers, such as, chronic lymphocytic leukemia (CLL). By targeting the BH3 domain of the family, multiple inhibitors have been created for cancer therapeutics¹¹¹. Some of these drugs developed are: ABT-737 (target BCL-2, BCL-XL, BCL-w)¹¹², ABT-263 or Navitoclax (target BCL-2, BCL-XL, BCL-w)¹¹³ have been tested in many clinical trials and has shown activity in CLL, bulky adenopathy etc. ABT-199 or venetoclax is the first selective oral BCL-2 inhibitor, and has shown anti-tumor activity against non-Hodgkin's lymphoma, CLL and acute leukemias¹¹⁴. Combination strategies with tyrosine kinase inhibitors and ABT-199 has also shown promise¹¹⁵. Clinical studies show that ABT-199 has an overall response rate of 84 % in 56 patients with relapsed or refractory CLL¹¹⁶. Although all these drugs on their own may not show an effective response, combination of different drugs that target multiple pathways may be an effective approach to improve their efficacy. Further, triple combination therapies that include radiation may further improve the efficacy of these agents, and increase the overall survival of the patients with limited toxicity concerns.

Immuno-Modulatory Agents and Checkpoint Blockade

Immunologic checkpoints expressed by T-cells, including CTLA-4 and PD-1 evolved to fine tune the adaptive immune response, reduce the probability for autoimmune disease, and maintain immunologic homeostasis.^{117–119} Due to the heavy selection pressure on developing malignancies by CD8⁺ T-cells,¹²⁰ cancer co-opts normal T-cell checkpoints to enhance tumor survival.¹²¹ Blockade of these checkpoints with monoclonal antibodies against the receptors on T-cells (anti-CTLA-4, anti-PD-1), or the tumor/tumor microenvironment expressed ligands (anti-PD-L1) has demonstrated remarkable clinical efficacy with approximately 30% of patients responding across tumor types.¹²² Biomarkers including tumor mutation burden, a surrogate for neoantigen load, and PD-L1 expression in the tumor/tumor microenvironment have been shown to predict for response to anti-PD-1/L1

treatment.^{123,124} Although these checkpoint inhibitors have shown great promise, the vast majority of patients still do not response, and therefore, combinatorial approaches with radiotherapy are being investigated.

Radiotherapy, although classically thought to be immunosuppressive, has been shown to stimulate an anti-tumor CD8⁺ T-cell response by inducing immunogenic cell death, type I interferon signaling, and upregulating/liberating neoantigens.^{125–127} In combination with checkpoint blockade, the radiotherapy stimulated immune response is enhanced¹²⁸ with occasional regression of tumors outside the irradiated field (abscopal effect).^{129–132} A recent elegant study by Formenti et al showed a response to radiotherapy plus anti-CTLA-4 in a chemo-refractory non-small cell lung cancer patient (NSCLC).¹³³ Detailed immunologic analysis demonstrated CD8⁺ T-cell recognition of a neo-antigen upregulated by radiotherapy.¹³³ Due to the enthusiasm from these preclinical and growing clinical data, a large number of combination clinical trials have been initiated. A phase I trial combining pembrolizumab (anti-PD-1) and stereotactic body radiotherapy (SBRT) in patients with metastatic solid tumors demonstrated an overall objective response rate of 13.2%. Interestingly a higher interferon- γ signature in the irradiated tumor correlated with a response in the nonirradiated tumor, suggestive of an abscopal effect.¹³⁴ Other studies in multiple cancer types including prostate cancer and NSCLC have also been suggestive of clinical synergy between radiotherapy and checkpoint blockade^{135–137}, however the optimal combination including dose, sequencing and appropriate fractionation are still under investigation.¹³⁰

Tumor Angiogenesis Modifiers

As tumors start growing progressively, they require abundant supply of nutrients and growth factors. To achieve this, they need a new vascular network in and around the tumor¹³⁸. This is achieved through the expression of pro-angiogenic growth factors, such as members of the vascular endothelial growth factors (VEGF)¹³⁹. VEGF is the key mediator of angiogenesis and binds to two main receptors, VEGFR1 and VEGFR2, expressed by endothelial cells¹⁴⁰. The unabated growth of tumor results in hypoxia. Hypoxia inducible factor (HIF) is the essential mediator of hypoxic response. HIF regulates many genes including VEGF, one of the primary target genes of HIF¹⁴¹. The production of VEGF and other growth factors result in new vasculature that is structurally and functionally abnormal, thus, allowing the tumor to grow exponentially. The blood vessels are irregular in shape, leaky, hemorrhagic with high interstitial pressure¹⁴². This results in irregular blood flow, hypoxia and thus more VEGF production. Due to these reasons, one or more of the VEGF subtypes is overexpressed in many solid tumors. Due to the central role of VEGF in angiogenesis, VEGF pathway represents an effective target for anti-angiogenic therapy for most tumors. Drugs such as bevacizumab, sunitinib and aflibercept have shown activity against some, but not all tumors by targeting VEGF¹³⁸. Need is to further understand how the vasculature can be effectively targeted in the tumors and if the combination of these drugs with agents such as radiation will improve outcomes. Radiation can decrease vasculature and even disrupt blood supply to the tumor causing tumor cell death. Under these condition, the use of VEGF inhibitors may be more effective to impede tumor growth even further and improving outcomes for patients more so, than the use of VEGF inhibitors alone and/or radiotherapy alone.

One retrospective study of 302 node negative breast cancer patients treated with only locoregional radiotherapy demonstrated that VEGF165 was a predictor of relapse free survival and overall survival, with the higher VEGF expressers doing worse and suggesting a more-radioresistant phenotype¹⁴³. Another study, in cervix cancer patients undergoing radiotherapy treatments, also concluded that pretreatment VEGF expressions may be an independent prognostic indicator of OS and metastases free survival¹⁴⁴. A preclinical study suggested that nelfinavir (which decreases VEGF expression) increased tumor regrowth assay in nude mice xenografts by causing a reduction in HIF-1alpha/VEGF expression and reduced tumor hypoxia⁴⁸. One clinical retrospective study in rectal cancer patients undergoing neoadjuvant radiotherapy suggested that pre-treatment VEGF measurements in tumors may be a useful marker for tumor response to preoperative radiotherapy¹⁴⁵. Those patients that higher mean VEGF expression had lower degree of complete tumor regression compared with those patient's tumors that had lower levels of VEGF expression¹⁴⁵. Furthermore, changes of serum VEGF levels in esophageal cancer,¹⁴⁶ lung patients,¹⁴⁷ cervical cancer¹⁴⁸ patients undergoing chemoradiotherapy may also provide some predictors of who may or may not do better. Drugs, such as ZD6474 (Zactima) that inhibit the VEGF pathway¹⁴⁹ may improve outcome in patients.

Radiation Countermeasures

Acute, accidental exposure to potentially lethal doses of ionizing radiation is a significant risk from nuclear reactors, munitions, and medical or industrial irradiators. Though less likely, military use of nuclear weapons can expose much larger numbers of victims. In a mass casualty setting, safe and effective therapies are needed that can prevent, mitigate and treat radiation toxicity. In turn, the safety profile must be high enough to allow treatment of any individual, including those unlikely to have been exposed to a toxic radiation dose. Development of novel medical countermeasures is underway that have the potential to satisfy these criteria with several agents demonstrating promising efficacy¹⁵⁰. Promising new drugs with FDA IND status include BIO 300, CBLB502/Entolimod, Ex-RAD, HemaMax, and Orbeshield.¹⁵¹ However, the slow pace of progress has raised the profile of repurposing as a promising route to practical radiation countermeasures.^{152,153} Two repurposed hematopoietic growth factors, filgrastim (G-CSF) and pegfilgrastim (PEGylated G-CSF), have been approved by the FDA using the animal rule.¹⁵⁴ Filgrastim was approved based on preclinical validation in mice, canine, minipigs and nonhuman primates.¹⁵⁵ The preclinical studies demonstrated increased survival and improved recovery of neutrophils after radiotherapy. G-CSF at 10 µg/kg/day increased the human primate survival after exposure to 7.5 Gy (LD_{50/60}) compared with vehicle controls, and decreased the duration of neutropenia¹⁵⁶. The authors found that the 60 day overall mortality was reduced from 59% down to 21%. Based on these studies, filgrastim was approved at 10 µg/kg/day for the management of hematological-acute radiation syndrome. PEGylated G-CSF involves the addition of a 20 kD monomethoxypolyethylene glycol (PEG) to the N-terminal methionine residue, and allows for a lower rate of clearance compared with G-CSF. After demonstrating benefits in reversing neutropenia and enhancing survival after total body irradiation in animal studies¹⁵⁷, PEGylated G-CSF was similarly FDA approved. A drawback of the hematopoietic growth factors is their high cost, requirement for *i.v.* administration, lack of

benefit for other aspects of radiation toxicity and limited potential for long-term storage. Multiple small molecule drugs approved for other indications that display attractive safety profiles are under consideration as radiation countermeasures, including pentoxifylline, statins, losartan, celecoxib, metformin, gabapentin and others^{150,158}.

Discussion

Radiation oncology has undergone tremendous changes and growth in terms of technological advances over the past decade. There has been increased emphasis on newer equipment that can more precisely localize tumors through image-guided approaches, as well as a focus on providing more conformal radiation treatments using intensity modulated (IMRT), volume modulated (VMAT), and proton radiotherapy approaches. Precision radiotherapy exploiting cone beam computerized tomography (CBCT), image guided radiotherapy (IGRT) using implanted fiducials and/or implant radiotherapy have become more common. Additionally, there has been increasing use of hypo-fractionated radiotherapy approaches using stereotactic localization with treatment of CNS tumors (stereotactic radiosurgery, SRS) and extra-cranial tumors (stereotactic body radiotherapy, SBRT). Many payers have accepted payment models that support the use of these radiotherapy advances. However, there continues to be a lack of emphasis on enhancing the radiation therapeutic index using combination approaches with existing drugs. Only a handful of drug combinations have been tested in phase III clinical trials, to date, most of which are cytotoxic drugs such as taxanes, platinum, gemcitabine, 5-fluorouracil, cetuximab, and temozolamide². Part of this may be related to lack of government funding and/or impetus provided by key stakeholders such as the Radiation Therapy Oncology Group (RTOG) and the National Cancer Institute of Health (NCI) to focus on multi-disciplinary approaches. However, the recent formation of the NRG Oncology Group may stimulate new attention to this issue². Furthermore, insurance payers may need to adapt their payment models, when radiotherapy is used in “combination” approaches that uses the underlying tumor biology to enhance the therapeutic index. The current models typically will reimburse for radiotherapy with the intent of either palliating and/or curing tumor with radiotherapy alone. In occasions, where a patient might benefit from concomitant treatment with radiotherapy and a drug, current payment models may separately pay for the cost of the drug, as it were being used alone, and pay for radiotherapy, when used alone. Thus, increased emphasis is needed by the key stake holders (funding agencies, pharmaceuticals, hospitals, and clinical trial agencies) to help encourage combination approaches with radiotherapy and oncogenic drugs.

Radiotherapy continues to be one of the most cost effective option for treatment of cancer, and around 60% of all patients will receive radiotherapy at some point during their course of cancer treatments¹. Besides advances in technology, combination approaches using refurbishing of drugs and/or new agents in combination with radiotherapy can further enhance the outcomes of patients in a more cost-effective and efficient way. Understanding the biology and mechanisms of action by which radiotherapy can control tumor growth, and what happens in the tumor micro-environment after radiotherapy can be exploited in combination with drug repurposing to improve outcome. We know that radiotherapy can lead to DNA double strand breaks, and things such as tumor hypoxia, tumor metabolism, engagement from the immune system after radiotherapy, and the impact of various growth

factors and angiogenesis are key to survival of the cancer cells after radiotherapy. Thus, drugs that can interrupt the oncogenic process either before, during, or after radiotherapy are critical to further enhancing post radiotherapy index. The new avenue of growth can also provide opportunities for repurposing of many drugs that are currently FDA approved.

Clearly, the development of new drugs can be time consuming, and immensely resource intensive. Drug development can take anywhere between 4 to 12 billion dollars, and the clinical development with radiotherapy may further add additional costs to this development². Furthermore, only about 40% of phase III trials in oncology are successful, and the overall success of a phase I trial achieving approval is mere 5.1%²; Lastly, it may take around 8 years, from opening the first monotherapy trial to publishing a successful phase III trial¹⁵⁹. Thus, there are many barriers to bringing in new drug combinations with radiotherapy, starting from initial chemistry/drug development stage, and then moving it into the preclinical and clinical stage. The chance, that a lead compound will makes it through all of the various phases, and eventually into a phase III clinical trials and become FDA approved to be combined with radiotherapy are minimal. However, many drugs that already exist can be repurposed for combination with radiotherapy. Prime examples include aspirin, metformin, statins, immune-checkpoint inhibitors, VEGF inhibitors, tumor hypoxia modifiers, and DNA double strand break repair modifiers. Repurposing of drugs can have several advantages: for one, drugs have already undergone the rigors of late stage clinical trials and have known safety data, there is huge money savings since repositioning a drug is clearly more cost effective, the repositioned drug may already have a market advantage with likely increased return on investment, and there are opportunities for out-licensing potential and could potentially out license the rights for new indications to other drug companies. The global impact of repositioning/repurposing of drugs in combination with radiotherapy are expected to be tremendous. Efforts by all key stake holders should help advance this new area of growth in the future.

Conclusions:

A tremendous opportunity remains to investigate drug combinations in the clinical setting that might increase the benefits of radiation without additional toxicity. We highlight many opportunities to apply repurposing, and survey candidate radiosensitizers that alter DNA repair, decrease hypoxia, block tumor survival signaling, modify tumor metabolism, block growth factor signaling, slow tumor invasiveness, impair angiogenesis, or stimulate anti-tumor immunity. These candidate drugs, some of which have been previously approved can confer radiation-enhancing effects, and may display low toxicity on their own. Promising agents include such widely used drugs as aspirin, metformin and statins, offering the potential to improve outcomes, decrease radiation doses and lower costs. In turn, repurposing radiation to enhance antibody drugs such as checkpoint blockade immunotherapies might increase their effectiveness, bringing their benefits to more patients. Additional focus by key stake holders is needed to help move many of these repurposed drugs from the shelf into the clinics. The benefits are expected to be tremendous to all stake holders, especially the radiotherapy patients.

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