Safety and Efficacy of Combination Targeted Therapy and Radiotherapy

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Abstract

Targeted cancer therapies that act on specific drivers of oncogenesis are rapidly entering clinical use. While many of these agents are ineffective at improving cure rates as monotherapy, there is ample preclinical evidence that they are both chemosensitizing and radiosensitizing, and can improve cure rates when utilized in combination treatment regimens. There is therefore a need for high-quality safety and efficacy data on targeted therapy in combination with radiation therapy (RT). This article reviews the currently published clinical trials examining the combination of RT with commonly used targeted agents, such as vascular endothelial growth factor inhibitors, endothelial growth factor receptor inhibitors, and inhibitors of the PI3K/Akt/mTOR pathway. Continued efforts to develop high-quality clinical trial data combining targeted agents with RT are necessary for patient safety and to improve clinical outcomes.

Key words: targeted therapies, radiation therapy, vascular endothelial growth factor inhibitors, PI3K, Akt, mTOR

Introduction

Radiation therapy (RT), together with surgery and chemotherapy, is one of the primary modalities used in definitive and palliative cancer treatment. Utilization analyses have revealed that RT is a part of initial treatment in approximately 30% of patients with cancer,[1] and approximately 50% of patients overall receive RT.[2] In comparing contribution toward cure by treatment modality, a European Union expert panel determined that cure is achieved in 49% of patients by surgery, 40% by RT, and 11% by chemotherapy.[3] Given these statistics and in light of advancements expanding the clinical indications of RT, RT will continue to be an essential modality in the treatment of malignancies in the future.

Targeted cancer agents that block specific molecular pathways involved in oncogenesis are rapidly shifting the landscape of cancer treatment. While these agents present promising opportunities for the treatment of many malignancies, the majority are cytostatic, and many impart modest, if any, survival benefit as monotherapy.[4,5] However, there is preclinical evidence that these agents are radiosensitizing and may improve cure rates when used in combination with RT.

The radiosensitizing effects of classical chemotherapeutics, including cisplatin, 5-fluorouracil (5-FU), taxanes, and temozolomide, have been well characterized, and the combination of such agents with RT has been demonstrated to improve survival and cure rates across many cancer types in randomized clinical trials.[6-18] Since these agents are nonspecific and radiosensitize normal tissue, such treatment carries greater toxicity. While this toxicity is accepted due to the even greater clinical benefit, targeted agents present an exciting opportunity because they may selectively radiosensitize tumor cells without a concomitant increase in normal tissue toxicity. In this review, we summarize the currently published clinical trials of commonly used therapies in combination with RT, with attention to data on efficacy and toxicity.

Hormone Therapy

Androgen-deprivation therapy (ADT) in combination with RT for prostate cancer can be viewed as an early targeted biologic approach. In 1997, the seminal Southwest Oncology Group (SWOG)/European Organisation for Research and Treatment of Cancer (EORTC) randomized trial demonstrated improved survival with the addition of goserelin to definitive RT for locally advanced prostate cancer.[17] Grade 3 or above acute and late toxicities were not significantly different with the addition of ADT. However, combined late grade 1-3 toxicities, including urinary incontinence and urethral stricture, were significantly increased in patients treated with ADT. Despite the higher rate of adverse effects (AEs) of combined therapy, this toxicity was deemed acceptable, and ADT with RT is currently an accepted standard of care for locally advanced prostate cancer.

Monoclonal Antibodies

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor A (VEGF-A), is a pioneering targeted agent that has been studied in large clinical trials.[19] A recently pub-

lished phase III trial utilizing bevacizumab with temozolamide and RT in glioblastoma multiforme improved progression-free survival (PFS) and quality-of-life endpoints, but not overall survival (OS).[20] The rates of grade ≥3 AEs were increased with the addition of bevacizumab. Interestingly, these toxicities were not primarily radiation-related. Instead, the majority were attributable to bevacizumab, and included thromboembolic events, bleeding events, impaired wound healing, gastrointestinal (GI) perforation, and congenital heart failure. Specifically, the rate of cerebral hemorrhage was increased in patients treated with bevacizumab compared with placebo (3.3% vs 2.0%). In rectal cancer, several early trials demonstrated the feasibility of using bevacizumab in combination with chemoradiation, with overall similar rates of AEs compared with historical controls.[21-24] However, increased GI bleeding thought to be due to the addition of bevacizumab was also observed in these studies.

For example, a phase II study from Canada reported severe preoperative bleeding events in 17% of patients treated with combination bevacizumab and chemoradiation.[23] In pancreatic cancer, two phase II trials evaluating the addition of bevacizumab to chemoradiation did not improve survival outcomes compared with historical rates.[25,26] Several bleeding events were noted with the addition of bevacizumab, but the sites of bleeding were outside of the radiation field. Ultimately, further studies are needed to determine the safety and efficacy of bevacizumab with chemoradiation and its application in the treatment of malignancies. Nevertheless, the data appear to support acceptable, though perhaps increased, toxicities of bleeding and thromboembolic events attributable specifically to bevacizumab.

Activating mutations of the EGFR/PI3K/Akt/mTOR pathway are common in cancers and have been implicated in radioresistance. The epidermal growth factor receptor (EGFR) inhibitor cetuximab has been found to have potent radiosensitizing properties in preclinical trials.[27] In a large, multi-institutional, randomized trial, Bonner et al[28] reported an OS benefit when adding cetuximab to RT in locally advanced head and neck squamous cell carcinoma (HNSCC). With the exception of acneiform rash and infusion reactions, the incidence of grade ≥3 toxicity did not differ significantly between patient arms. This trial demonstrated the feasibility, safety, and efficacy of adding cetuximab to RT. However, the follow-up study, RTOG 0522, which added cetuximab to cisplatin-based chemoradiation for locally advanced HNSCC, did not show a survival benefit with the addition of cetuximab.[29] Indeed, patients who were treated with cetuximab in addition to cisplatin had more interruptions in RT, increased treatment-related death, and increased grade ≥3 AEs, including mucositis and anorexia.

Similarly, a recently reported randomized phase III trial for stage IIIA/B non–small-cell lung cancer (NSCLC), RTOG 0617, demonstrated no clinical benefit with the addition of cetuximab to standard or dose-escalated chemoradiation.[30] However, patients receiving cetuximab in addition to chemoradiation experienced significantly higher rates of grade ≥3 toxicities compared with those receiving chemoradiation alone (86% vs 70%). Further, there were more treatment-related deaths with the use of cetuximab (4.2% vs 2.2%).

A related EGFR antibody, panitumumab, has been examined in the randomized phase II trials for HNSCC, CONCERT-1,[31] and CONCERT-2.[32] CONCERT-2 compared panitumumab plus RT to cisplatin-based chemoradiation in patients with locally advanced HNSCC. This study demonstrated inferior local control at 2 years in those receiving panitumumab (51% vs 61%). Toxicities were considered to be similar between the groups, with the exception of increased skin toxicity in the panitumumab group (24% vs 11%). CONCERT-1 examined panitumumab plus cisplatin-based chemoradiation compared with chemoradiation alone. This trial demonstrated no additional benefit with the addition of panitumumab. There were more treatment breaks and grade ≥3 AEs in the panitumumab arm, most commonly mucosal inflammation (55% vs 24%), radiation dermatitis (28% vs 13%), and dysphagia (39% vs 27%). There was one treatment-related death in each arm in this trial.

Small-Molecule Inhibitors

Erlotinib, an EGFR small-molecule inhibitor, has been shown to be well tolerated in combination with: capecitabine and RT in locally advanced pancreatic cancer[33]; capecitabine, bevacizumab, and RT in rectal cancer[34]; and RT in esophageal cancer.[35] A phase II trial combining erlotinib with stereotactic body RT for patients with progressive metastatic NSCLC demonstrated improved PFS and OS compared with historical controls, and was well tolerated, with only two of 24 RT-related grade 3 toxicities.[36] Similarly, a phase II trial of erlotinib combined with temozolomide in addition to RT in glioblastoma multiforme reported better survival than historical controls and an acceptable safety profile.[37] However, a randomized phase II trial comparing erlotinib plus cisplatin-based chemoradiation with chemoradiation alone in patients with locally advanced HNSCC demonstrated no difference in clinical complete response rates between the two groups.[38] The addition of erlotinib did not increase the rate of AEs overall, but patients receiving erlotinib experienced a higher rate of grade 3 rash (13% vs 2%). Sunitinib, a multikinase inhibitor, has been shown to be well tolerated when combined with ADT and RT in localized high-risk prostate cancer,[39] in combination with RT for central nervous system (CNS) malignancies,[40] and for oligometastatic disease,[41] with good clinical responses in phase I and II studies.[41]

The proteasome inhibitor bortezomib may radiosensitize tumors by blocking DNA repair and has been examined in several phase I and II trials.[42] In a phase I/II trial examining the addition of bortezomib to carboplatin, paclitaxel, and RT for stage III NS-

TABLE Summary of Clinical Trials Combining Radiation Therapy and Targeted Agents

Mechanism	Drug	Trial	Tumor	Phase	Study Size (n)	Treatment	Outcome
Androgen deprivation	Goserelin	Bolla et al. (1997)	Prostate cancer	III	401	70 Gy +/- goserelin	Improved 5-year survival. Increased rates of thromboembolism and bleeding toxicities, but not overall toxicity
Anti-VEGF monoclonal antibody	Bevacizumab	Chinot et al. (2014)	Glioblastoma multiforme	III	921	60 Gy + temozolomide +/-bevacizumab	Improved progression-free survival and quality of life, no improvement in overall survival. Increased grade 3 or above adverse events attributable to bevacizumab
		Czito et al. (2007)	Rectal cancer	I	11	Preoperative 50.4 Gy + capecitabine + oxaliplatin + bevacizumab	Accepetable toxicity and promising tumor regression
		Kennecke et al. (2012)	Rectal cancer	II	42	Preoperative 50.4 Gy + capecitabine + oxaliplatin + bevacizumab	Treatment was well tolerated with promising tumor regression. 17% preoperative bleeding event rate. Results did not justify a phase III trial
		Spigel et al. (2012)	Rectal cancer	II	66	50.4 Gy + 5-FU + bevacizumab; FOLFOX6 following surgery (neoadjuvant cohort) or chemoradiation (adjuvant cohort)	Promising disease-free survival and acceptable toxicity in both the neoadjuvant and adjuvant setting. 15% grade 3-4 thromboembolism rate
		Velenik et al. (2011)	Rectal cancer	II	61	preoperative 50.4 Gy + capecitabine + bevacizumab	Lower pathologic complete response rate compared to historical controls. Acceptable toxicity
		Crane et al. (2009)	Pancreatic cancer	II	82	50.4 Gy + capecitabine + gemcitabine + bevacizumab	Similar survival to historical controls. 6.1% bleeding event rate (all outside tumor site) and 1/10 major postoperative complication rate; otherwise well tolerated
		Small et al. (2011)	Pancreatic cancer	II	28	36 Gy + gemcitabine + bevacizumab	Similar survival to historical controls. Treatment was well tolerated with 1/10 major postoperative complication rate
Anti-EGFR monoclonal antibody	Cetuximab	Bonner et al. (2010)	HNSCC	III	424	72 Gy +/- cetuximab	Overall survival benefit to cetuximab, with no increased toxicity in cetuximab arm
		Ang et al. (2014)	HNSCC	III	891	70-72 Gy + cisplatin +/- cetuximab	No survival benefit with the addition of cetuximab. Increased rates of grade 3 and above acute toxicity and treatment-related deaths in patients treated with cetuximab
		Bradley et al. (2015)	NSCLC	III	544	60-74 Gy + paclitaxel + carboplatin +/- cetuximab	No survival benefit with the addition of cetuximab. Increased rates of grade 3 or above toxicity and treatment-related deaths in patients treated with cetuximab
	Panitumumab	Mesia et al. (2015)	HNSCC	II	153	70 Gy + cisplatin +/- panitumumab	No survival benefit with the addition of panitumumab. More treatment breaks and skin and mucosal toxicity in the panitumumab arm
		Giralt et al. (2015)	HNSCC	II	152	70-72 Gy + cisplatin or panitumumab	Lower local-regional control and survival in the panitumumab arm. More treatment breaks, skin toxicity, and treatment-related deaths in the panitumumab arm

HNSCC indicates head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy.

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TABLE Summary of Clinical Trials Combining Radiation Therapy and Targeted Agents (*continued*)

Mechanism	Drug	Trial	Tumor	Phase	Study Size (n)	Treatment	Outcome
EGFR small molecule inhibitor	erlotinib	Jiang et al. (2014)	pancreatic cancer	I	15	50.5 Gy + capecitabine + erlotinib	Treatment was well tolerated with similar survival to historical controls
		Das et al. (2014)	rectal cancer	I	18	preoperative 50.5 Gy + capecitabine + bevacizumab + erlotinib	Improved pathologic complete response rate and disease-free survival over historical controls. Treatment was well tolerated
		Iyer et al. (2013)	esophageal cancer	II	17	50.4 Gy + erlotinib	Treatment was well tolerated, with grade 3-4 adverse events in 29% of patients
		Iyengar et al. (2014)	metastatic NSCLC	II	24	SBRT* (variable) + erlotibinib	Improved progression-free and overall survival over historical controls. Treatment was well tolerated
		Prados et al. (2009)	glioblastoma multiforme/ gliosarcoma	II	65	59.4-60 Gy + temozolomide + erlotinib	Improved progression-free and overall survival over historical controls. Treatment was well tolerated
		Martins et al. (2013)	HNSCC	II	204	70 Gy + cisplatin +/- erlotinib	No survival benefit with the addition or erlotinib. Similar toxicity overall, but more grade 3 or above skin toxicity with erlotinib
Multikinase small molecule inhibitor	sunitinib	Corn et al. (2013)	prostatic cancer	I	17	75.6 Gy + leuprolide or goserelin + sunitinib	Feasibility of treatment was established
		Wuthrick et al. (2011)	metastatic CNS malignancies	I	15	14-70 Gy + sunitinib	Improved progression-free survival over historical controls. Treatment was well tolerated
		Tong et al. (2012)	oligometa-stases	II	25	50 Gy + sunitinib	Durable complete clinical and radiographic remissions were observed. Toxicities were manageable but greater than reported in trials of radiation alone
Proteasome small molecule inhibitor	bortezomib	Zhao et al. (2015)	NSCLC	I/II	27	60 Gy + paclitaxel + carboplatin + borte-zomib	Improved overall survival compared to historical controls. There were increased grade 3-4 hematologic toxicities but treatment was tolerated overall
		Pugh et al. (2010)	metastatic solid malignancies (palliative)	I	12	40 Gy + bortezomib	Feasibility of treatment was established
		Kubicek et al. (2009)	CNS malignancies	I	27	30-66 Gy+ temozolo-mide + bortezomib	Favorable median survival in newly diag-nosed patients compared to historical controls. Treatment was well tolerated with no dose-limiting toxicities
		O'Neil et al. (2010)	rectal cancer	I	9	preoperative 50.4 Gy + 5-FU + bortezomib	Grade 3-4 diarrhea limited dose to non-biologically meaningful level
		Argiris et al. (2011)	HNSCC	I	7	70-74 Gy + cetuximab + bortezomib	Therapy was tolerated but progres-sion-free survival was decreased compared to historical controls
		Ree et al. (2010)	gastroin-testinal carcinoma (palliative)	I	16	30 Gy + vorinostat	Most adverse events were grade 1-2, but there was more grade 3 toxicity than observed with monotherapy. Authors concluded treatment was tolerable
		Shi et al. (2014)	CNS metastases	I	13	37.5 Gy + vorinostat	Treatment was well tolerated with no treatment-related toxicities over grade 2

HNSCC indicates head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy.

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TABLE Summary of Clinical Trials Combining Radiation Therapy and Targeted Agents (*continued*)

Mechanism	Drug	Trial	Tumor	Phase	Study Size (n)	Treatment	Outcome
mTOR small molecule inhibitor	Everolimus	Deutsch et al. (2015)	NSCLC	I	21	66 Gy + everolimus followed by cisplatin + navelbine	Favorable partial response rate and 2-year survival. Grade 3-4 interstitial pneumonitis in 24% of patients
		Ma et al. (2014)	Glioblastoma multiforme	II	100	60 Gy + temozolomide + everolimus	Similar survival to historical controls. 43% of patients had a grade 3-4 non-hematologic adverse event
		Sarkaria et al. (2011)	Glioblastoma multiforme	I	18	60 Gy + temozolomide + everolimus	43% of patients experienced grade 3-4 toxicity, but overall treatment was reasonably well tolerated
		Fury et al. (2013)	HNSCC	I	13	60-70 Gy + cisplatin + everolimus	Treatment was well tolerated with grade 3 or above lymphopenia in 92% of patients, and dose-limiting toxicities of mucositis and failure to thrive in three patients
Akt pathway small molecule inhibitor	Nelfinavir	Brunner et al. (2008)	Pancreatic cancer	I	12	59.4 Gy + cisplatin + gemcitabine + nelfinavir	Favorable treatment response rate compared to historical controls. No additional nelfinavir-related toxicity occurred, and there was no grade 3 or above radiation-related toxicity
		Buijsen et al. (2013)	Rectal cancer	I	11	preoperative 50.4 Gy + capecitabine + nelfinavir	Therapy was deemed feasible, but 64% of patients experienced a grade 3-4 adverse event
	Enzastaurin	Butowski et al. (2010)	Glioblastoma multiforme	I	12	60 Gy + temozolomide + enzastaurin	Treatment was well tolerated with grade 3-4 thrombocytopenia the only dose-limiting toxicity

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CLC, patients tolerated treatment overall, but had more grade 3 or 4 hematologic toxicities.[43] Similarly, a phase I trial looking at bortezomib concurrent with palliative RT in patients with metastatic solid cancers demonstrated feasability, with patients most commonly experiencing hematologic AEs.[44] Another phase I trial examining bortezomib plus concurrent temozolomide and RT for CNS malignancies demonstrated safety, with no dose-limiting toxicities noted.[45] Conversely, a phase I trial adding bortezomib to chemoradiation for rectal cancer demonstrated an increased rate of dose-limiting toxicities (defined as grade ≥3 diarrhea).[46] This limited the maximum tolerated dose to the first dosage level of the study, which was not considered to be biologically meaningful. Interestingly, and as a note of caution in combining biologic therapies, a phase I trial combining bortezomib with cetuximab and RT in HNSCC showed increased rates of early progression of disease compared with cetuximab and radiation historical controls.[47] Biologic correlates of the trial demonstrated enhanced EGFR prosurvival signaling with bortezomib, likely counteracting the therapeutic effect of cetuximab and RT.

Histone deacetylase (HDAC) inhibitors may also radiosensitize tumors via DNA repair inhibition,[48] and have been examined in early-phase clinical trials. In the phase I PRAVO trial,[49] which examined vorinostat in the context of palliative pelvic radiation, the majority of AEs were grade 1 or 2. Grade 3 or higher treatment-related toxicities of fatigue and anorexia were noted. The authors of this study concluded that vorinostat can be safely combined with palliative pelvic RT. A phase I trial demonstrated that the combination of vorinostat with whole-brain RT for brain metastases is safe and well tolerated, with no treatment-related toxicities above grade 2.[50] Taken together, these findings are encouraging for the potential use of HDAC inhibitors in curative RT.

mTOR inhibitors have been shown to be potent radiosensitizers.[51] One recent phase I trial combining everolimus with thoracic RT in NSCLC reported grade 3-4 interstitial pneumonitis in 5 of 21 patients.[52] The authors concluded that pulmonary toxicities were of concern and should be carefully monitored. A phase II trial of everolimus, temozolomide, and RT in patients with glioblastoma multiforme did not demonstrate a survival benefit compared with historical controls, with "moderate toxicity" of 12% grade ≥4 nonhematologic toxicities and one treatment-related death out of the 100 patients enrolled to the study.[53] A previous phase I study suggested that the dose-limiting toxicities, including fatigue, hematologic toxicity, and liver dysfunction, were not related to RT.[54] In the context of patients with HNSCC, a phase I study of everolimus, cisplatin, and RT showed

the combination to be well tolerated, with the expected dose-limiting toxicities of mucositis and failure to thrive in three patients.

The use of Akt pathway inhibitors also has been studied in limited clinical trials. A phase I trial of the Akt pathway inhibitor nelfinavir and chemoradiation for locally advanced pancreatic cancer demonstrated no grade ≥3 radiation-related AEs, and the addition of nelfinavir was felt to have acceptable toxicity and promising activity.[55] Another phase I trial examined the safety of nelfinavir combined with chemoradiation for locally advanced rectal cancer.[56] Of the 11 patients analyzed, three had grade 3 diarrhea, two had grade 3 transaminitis, one had grade 3 cholangitis, and one had a grade 4 postoperative wound infection. No dose-limiting toxicities were noted at the beginning dosage level, so this dosage was recommended for phase II trials. Finally, a phase I trial adding enzastaurin, a PKC-β and PI3K/Akt pathway inhibitor, to temozolomide and RT for glioblastoma multiforme showed good tolerance, with grade ≥3 thrombocytopenia in two patients being the only dose-limiting toxicity.[57]

Immunomodulators

There are promising novel biologic rationales for combining immunomodulators with RT. Radiation may stimulate the immune response when combined with immunomodulators.[58,59] In particular, checkpoint inhibitors such as anti-CTLA-4 and anti-PD-L1/PD-1 have shown great promise in combination with RT.[59,60] Ongoing early clinical trials currently are studying combining RT and immunomodulators.

Conclusion

This review underscores an underrepresentation of RT in targeted therapy clinical trials, despite the common use of RT in cancer treatment. Approximately 70 novel targeted cancer therapies are currently approved by the US Food and Drug Administration, with hundreds more in development. Many of these agents have been demonstrated in the preclinical setting to enhance the radiation effect; however, the majority have not been investigated in even phase I clinical trials for safety in the context of RT. The published clinical trials reviewed here suggest that it is feasible to combine targeted agents with RT. However, there are many single institutional case series that have provided mixed data, with some suggesting safety and others suggesting unexpected toxicities.[61,62] One recent analysis demonstrated that of the over 400 phase I trials published yearly, only 30 include RT.[63] There is clearly a deficit of high-quality clinical data to guide the care of patients with cancer who are treated with targeted agents, and who have an indication for RT. To begin to address the lack of combined RT phase I trials, guidelines have been published by the National Cancer Institute,[64] Radiation Therapy Oncology Group,[4] and National Cancer Research Institute[65] emphasizing the importance of such studies and considerations of trial design and optimization. Such development of clinical trial data will ensure safe patient care and optimization of combined therapy treatment strategies.

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