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Critical Review

Safety and Tolerability of Metastasis-Directed Radiation Therapy in the Era of Evolving Systemic, Immune, and Targeted Therapies

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Abstract

Purpose Systemic, immune, and target therapies are growing in use in the management of metastatic cancers. The aim of this review was to describe up-to-date published data on the safety and tolerability of metastasis-directed hypofractionated radiation therapy (RT) when combined with newer systemic, immune, and targeted therapies and to provide suggested strategies to mitigate potential toxicities in the clinical setting.

Methods and Materials: A comprehensive search was performed for the time period between 1946 and August 2021 using predetermined keywords describing the use of noncentral nervous system palliative RT with commonly used targeted systemic therapies on PubMed and Medline databases. A total of 1022 articles were screened, and 130 met prespecified criteria to be included in this review.

Results: BRAF and MEK inhibitors are reported to be toxic when given concurrently with RT; suspension 3 days and 1 to 2 days, respectively, prior and post-RT is suggested. Cetuximab, erlotinib/gefitinib, and osimertinib were generally safe to use concomitantly with conventional radiation. But in a palliative/hypofractionated RT setting, suspending cetuximab during radiation week, erlotinib/gefitinib 1 to 2 days, and osimertinib ≥2 days pre- and post-RT is suggested. Vascular endothelial growth factor inhibitors such as bevacizumab reported substantial toxicities, and the suggestion is to suspend 4 weeks before and after radiation. Less data exist on sorafenib and sunitinib; 5 to 10 days suspension before and after RT should be considered. As a precaution, until further data are available, for cyclin-dependent kinase 4-6 inhibitors, consideration of suspending treatment 1 to 2 days before and after RT should be given. Ipilimumab should be suspended 2 days before and after RT, and insufficient data exist for other immunotherapy agents. Trastuzumab and pertuzumab are generally safe to use in combination with RT, but insufficient data exist for other HER2 target therapy.

Conclusions: Suggested approaches are described, using up-to-date literature, to aid clinicians in navigating the integration of newer targeted agents with hypofractionated palliative and/or ablative metastatic RT. Further prospective studies are required.

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Introduction

The use of cancer-directed therapy is rapidly advancing in the era of individualized patient directed care and with the emergence of numerous systemic, immune, and targeted therapies. For patients with metastatic disease, the role of radiation therapy (RT) is also evolving, with increasing interest in combining radiation with these newer systemic therapies to potentiate an antitumor immune response and in an effort to avoid interruptions of systemic treatment in patients with metastatic disease.[1-3]

Limited prospective safety and tolerability data exist for combining systemic therapies and RT in the metastatic setting. The aim of this review was to describe up-to-date published data on the safety and tolerability of metastasis-directed hypofractionated RT when combined with newer systemic, immune, and targeted therapies and to provide suggested strategies to mitigate potential toxicities in the clinical setting.

Methods and Materials

A comprehensive literature review from peer-reviewed journals was performed through PubMed and Medline from 1946 to August 2021. The search strategy was restricted to English language and human subjects, with subject-specific keywords developed as per authors' consensus (EG, AB). Controlled vocabulary terms were used when available, referring to palliative RT, stereotactic body RT (SBRT), bone metastases, targeted therapy, check-point inhibitor, BRAF inhibitor, MEK inhibitor, immunotherapy, programmed cell death-1 (PD-1) inhibitor, programmed cell death ligand (PDL-1) inhibitor, tyrosine kinase inhibitor, and cyclin-dependent kinase 4-6 inhibitor (see Supplementary Materials; Appendix 1 for complete list). The most recent search was performed May 17, 2022. Of 1029 screened articles, only prospective studies, retrospective studies, and case reports where the aforementioned treatments and RT were used concomitantly or sequentially with discussion of radiation-induced toxicity were reviewed. A limited number of articles using conventional nonmetastatic RT combined with contemporary systemic therapies are discussed in this paper where there was an absence of data in the palliative RT or SBRT setting. A total of 907 studies were excluded where RT to the central nervous system was delivered or radionuclide therapy was used and safety data were not available. A further 8 publications were added from the authors' own libraries. A total of 130 publications were selected.

Publications including typically used palliative and/or metastatic-directed RT fractionation regimens − moderate (defined as >2.2 Gy per fraction [fr]) and ultrahypofractionation (defined as ≥5 Gy per fr [≤10 fr],[4] with SBRT specified as ≤6 fr) − were included in this analysis. These 2 regimens are typically used in the palliative and metastatic disease setting. The toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE v3.0 or higher)[5] when information was available.

Results

Publications were divided according to class of systemic agent. Based on the limited data available, suggested toxicity mitigation strategies were proposed (Table 1) for each class. When relevant palliative studies were not available, curative intent trials were primarily used, and, finally, when neither of these were available, the drug's elimination half-life (as it leads to the elimination of more than 95% of the drug[6]) was considered to guide clinical practice.

RT and BRAF/MEK inhibitor agents

Vemurafenib and dabrafenib are the 2 most commonly used BRAF inhibitors, mainly in the management of metastatic melanoma. They are shown to be associated with in vitro radiosensitization[7,8] and have a $t^1/_2$ of 57 hours[9] (range, 30-120 hours) and 8 hours,[9] respectively.

When BRAF inhibitors are combined with RT, the most commonly report side effect is dermatitis, occurring during or within 7 days of RT.[10-23] In addition to acute skin toxicities, there have been a number of case reports of radiation recall associated with systemic agents that have started more than 7 days from RT completion, with no CTCAE grade 3 or higher toxicity reported, and subsequently they were managed conservatively.[10,24-29] All CTCAE grade 3 toxicities happened when the BRAF inhibitor was given concurrently or within 2 days of radiation[15] and when high-dose RT was given (eg, 71 Gy in 28 fr).[27] A dose threshold has not been reported, but from retrospective data by Churilla et al,[30] when treating with 30 Gy in 10 fr, the estimated dose received by the skin was 23 to 31 Gy, resulting in a grade 3 dermatitis.

Nondermatologic toxicities are less commonly reported in the literature (Supplementary Materials; Appendix 9). Anker et al[15] reported a CTCAE grade 5 hepatic hemorrhage, which occurred after 20 Gy in 5 fr using parallel opposed beam radiation delivered to T10 to L1 vertebral body. However, the direct causality was unclear due to the growing number and size of known liver metastases, and the low dose of radiation received by the liver (liver mean dose = 2.7 Gy). Underlying liver function was not reported, but additional data suggest avoiding direct liver irradiation when patients on BRAF inhibitors present with a Child-Pugh B7 and higher

Table 1 Summary of suggested approaches

Agents	Drug	Suggestions
BRAF and MEK inhibitor	Vemurafenib and dabrafenib; trametinib	Suspend 3 d before and after RT. Suspend 1-2 d before and after RT.
EGFR and ALK inhibitor	Cetuximab; erlotinib and gefitinib; crizotinib and osimertinib	Suspend the week of radiation if SBRT. Suspend 1-2 d before and after RT. Suspend ≥2 d before and after RT.
VEGF inhibitor	Bevacizumab; sorafenib and sunitinib	Suspend 4 d before and after RT. Suspend 5-10 d before and after RT.
Cyclin-dependent kinase (CDK) inhibitors 4-6	Palbociclib and ribociclib	Suspend 3 d before and after RT.
Immunotherapy	Ipilimumab; other	Suspend 2 d before and after RT if 8 Gy in single fraction to bone. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis.
HER2 target therapy	Trastuzumab and pertuzumab; lapatinib; T-DM1	Generally safe to use concomitantly with RT. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis.

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; RT = radiation therapy; SBRT = stereotactic body RT; VEGF = vascular endothelial growth factor; CDK = cyclin-dependent kinase; TDM1 = trastuzumab emtansine.

score.[31] A CTCAE grade 5 toxicity, reported by Baroudjian et al,[11] resulted in a hemothorax 1 month after palliative right axillary RT using 20 Gy in 4 fr. Reassuringly, they also reported another similar case that had no toxicities with a higher dose of 30 Gy in 6 fr. Two cases of CTACE grade 2 pneumonitis with combined vemurafenib and chest irradiation were reported, but the authors were unable to differentiate if toxicities were solely drug related or not.[32] A patient who received concurrent vemurafenib with palliative RT to the left neck, 50 Gy in 20 fr, developed a CTCAE grade 3 oral mucositis and dermatitis.[12] According to the authors, this toxicity was not expected, with the oral cavity receiving at most 12 Gy. Hecht et al[16] reported only 2 patients (2%) with grade 3 esophagitis with parenteral nutrition needs in their series on spine irradiation in patients with melanoma.

Trametinib is a MEK-inhibitor targeting the MAPK pathway, used frequently in combination with dabrafenib and mainly used in melanoma and anaplastic thyroid cancer. It has a $t^1/_2$ of 4 to 5 hours.[9] Therefore, little information on the use as a monotherapy exists.

A recent phase 2 study by Zhu et al[33] compared pancreatic cancer SBRT 35 Gy in 5 fr, in the setting of locally recurrent pancreatic cancer, with pembrolizumab and trametinib versus gemcitabine concurrently. Reported toxicities were more commonly seen in the SBRT plus pembrolizumab and trametinib arm, with CTCAE grade 3 to 4 increased liver enzymes (12% vs 7%) and increased bilirubin (5% vs 0%), with no treatment-related deaths. However, hepatotoxicity is not a common side effect of trametinib, and the authors believed the reported toxicity likely arose from the pembrolizumab. No toxicities have been reported with this drug combination with conventional RT.[34] A case of CTCAE grade 4 bowel perforation was described at 1 month after palliative RT (20 Gy in 5 fr) with dabrafenib and trametinib, which was started 10 days after radiation.[29]

A recent phase I/II study[35] evaluated the use of dabrafenib and trametinib in patients with metastatic melanoma receiving palliative radiation (20 Gy in 5 fr and 30 Gy in 10 fr). Two patients included in the study received 20 Gy in 5 fr using 3-dimensional conformal RT to the lumbar spine and right ilium/L1 vertebra, respectively, without any significant gastrointestinal (GI) toxicities reported by 12 months.

Summary and suggested toxicity mitigation strategies

Guidelines from the Eastern Cooperative Oncology Group and based on data outlined previously, suspension of BRAF inhibitors 3 days before and after radiation[29] should be considered mainly to avoid skin toxicity. There are insufficient published data to provide a recommendation for MEK inhibitors. Based on trametinib's $t^1/_2$, 1 to 2 days pre- and post-RT might be sufficient.

RT and epidermal growth factor receptor/ anaplastic lymphoma kinase inhibitor agents

Commonly used epidermal growth factor receptor inhibitors include cetuximab, erlotinib, gefitinib, and osimertinib, with $t^1/_2$ of 112, 36.2, 48, and 48 hours, respectively.[9] Cetuximab is a monoclonal antibody targeting epidermal growth factor receptor, whereas the other agents are receptor tyrosine kinase inhibitors (TKIs). Crizotinib is an anaplastic lymphoma kinase inhibitor with $t^1/_2$ of 42 hours.[9] Anaplastic lymphoma kinase TKIs have been reported to potentiate the effect of lung injury when the lungs are within the RT target volume.[36] Studies primarily involving the use of these agents in combination with RT for the treatment of head and neck, colorectal, and non-small cell lung cancer (NSCLC) are summarized in Supplementary Materials; Appendix 4.

There are a lack of data reporting the use of cetuximab combined with hypofractionated and/or palliative RT. The majority of evidence describes cetuximab in combination with radical, conventionally fractionated RT for locally advanced head and neck cancer. These studies report a 6% to 36% risk of CTCAE grade 3 or higher skin reaction, which is significantly increased with cetuximab compared with cisplatin.[37-40] In the palliative setting, only 1 case has reported a grade 3 esophagitis when fluorouracil/cisplatin and cetuximab were combined with 30 Gy in 10 fr spine RT.[41] A retrospective study reported no CTCAE grade 3 or higher toxicity[42] when hypofractionated RT was used in 3 patients with metastatic head and neck cancer.[42] Other studies reporting head and neck SBRT delivered concomitantly with cetuximab were in recurrent settings.[43-45] Concomitant cetuximab with conventionally chest fractionated thorax RT has been studied in 2 phase 2 studies without major safety concerns[46,47] and with conventionally fractionated RT to the rectum with a 5% to 38% rate of CTCAE grade 3 to 4 diarrhea.[48]

Numerous prospective studies have investigated the role of conventionally fractionated RT in combination with erlotinib and gefitinib, reporting CTCAE grade ≤3 toxicities related to nausea, skin, esophagitis, and pneumonitis.[49-60] Weickhardt et al,[61] Gan et al,[62] and Borghetti et al[63] published retrospective studies treating different metastatic sites from GI cancers with concurrent erlotinib or crizotinib using SBRT and hypofractionated palliative RT, and no CTCAE grade 3 or higher toxicity was reported. In the multi-institutional phase II study by Gomez et al,[1] which treated patients with oligometastatic NSCLC without progression after front-line systemic therapy, 2 patients received SBRT concurrently with crizotinib, and reported toxicities were similar to patients who did not receive concomitant therapy. Gefitinib was also used in combination with lung SBRT in a retrospective study of 122 elderly patients with no pneumonitis reported.[64] In a phase II trial by Swanimath et al,[65] the safety of palliative hypofractionated thorax RT (30 Gy in 10 fr) with concurrent erlotinib was demonstrated, with only 1 CTCAE grade 3 nausea and 1 CTACE grade 4 dermatitis reported. However, a Chinese study published a high rate of CTCAE grade 3 or higher radiation pneumonitis (54%), including 1 death, when osimertinib was combined with palliative lung RT (30-60 Gy in 10-30 fr).[52]

Summary and suggested toxicity mitigation strategies

Cetuximab is commonly used with conventionally fractionated RT; however, in the setting of hypofractionated RT, due to the long $t^1/_2$ and paucity of toxicity data, omitting it during the week of radiation treatment is suggested. Erlotinib and gefitinib have been reported as safe with conventionally fractionated RT, but in the absence of supportive data in the setting of palliative/metastasis-directed RT, a washout period of 1 to 2 days before starting radiation is suggested. Due to lack of prospective data, combining crizotinib or osimertinib with RT is cautioned, and a washout period of at least 2 days is recommended. In cases where radiation is delivered to the lung, attention should be given to lung dosimetry, especially in the setting of patients with interstitial pneumonitis.

Vascular endothelial growth factor inhibitor agents

Bevacizumab is a humanized monoclonal antibody that binds and neutralizes vascular endothelial growth factor (VEGF)-A with a $t^1/_2$ of 20 days.[9] It is most commonly used in the management of gynecologic, colorectal, and hepatocellular malignancies (Supplementary Materials; Appendix 5).

Bleeding after surgery in patients receiving bevacizumab is commonly reported. A meta-analysis[66] described the incidence of GI perforation at 1% with an associated mortality rate of 21% in patients receiving bevacizumab, with history of prior radiation reported as a risk factor. Barney et al[67] further reported a 9% rate of serious bowel injury (CTCAE grade 3-4 GI ulceration, CTCAE grade 4-5 GI perforation) post-SBRT (median dose, 50 Gy in 5 fr) in patients who received VEGF inhibitors before and after radiation, with reported toxicities higher (up to 35%) when systemic therapy was given after radiation. No clinically significant CTCAE grade 3 or higher bowel toxicities occurred in patients not receiving VEGF inhibitor after SBRT. These findings suggest a synergistically deleterious effect with the combination of VEGF inhibitors and SBRT. Note that no toxicities were reported when a maximum bowel dose of 18 Gy was recorded.

Sorafenib and sunitinib are multireceptor TKIs targeting, among others, the kinase c-raf, VEGFfr 2/3, and platelet-derived growth factor-αl, with a $t^1/_2$ of 25 to 48

and 40 to 60 hours, respectively.[9] These agents are mostly used in hepatocellular carcinoma, renal cell carcinoma, GI stromal tumor, and thyroid carcinoma (Supplementary Materials; Appendix 5).

Peters et al[68] reported a CTCAE grade 5 bowel perforation with a single dose of palliative RT to the spine (8 Gy in 1 fr) when sorafenib was stopped 2 days before radiation and restarted 3 days post. Murray et al[69] reported severe toxicities with concurrent sorafenib and palliative radiation (30 Gy in 10 fr), as 1 CTCAE grade 3 esophagitis, 1 CTCAE grade 3 transaminase elevation, and 1 CTCAE grade 5 bowel perforation (tumor was invading the bowel in this case). Two phase I studies[70-71] showed that concurrent sorafenib with liver SBRT resulted in clinically meaningful toxicities, such as GI bleeding.

A phase II trial[72] published important GI toxicities associated with a combination of sunitinib and SBRT (50 Gy in 10 fr) for oligometastatic disease. Also, Staehler et al[73] studied the association of sorafenib and sunitinib with spine stereotactic radiosurgery (20 Gy in 1 fr), reporting 1 CTCAE grade 3 bleed and 1 CTCAE grade 5 GI hemorrhage that was considered likely related to sunitinib rather than RT.

Summary and suggested toxicity mitigation strategies

Combining VEGF-inhibitor agents with any fractionation schedule of radiation appears unsafe. Bevacizumab should be stopped at least 4 weeks before RT and recommence at least 4 weeks post-RT. For TKIs targeting VEGF, at least 5 to 10 days pre- and post-RT should be considered, especially if GI mucosa is within the irradiated field.

CDK4-6 inhibitor agents

Palbociclib is a reversible small molecule cyclin-dependant kinase inhibitor selective for CDK 4 and 6, which has a role in regulating progression through the cell cycle and has a $t^1/_2$ of 29 hours.[9] Ribociclib and abemaciclib are CDK 4 to 6 inhibitors with $t^1/_2$ of 30 to 55 hours and 18.3 hours.[9]

Few retrospective data[74-81] exist on the use of CDK4/6 inhibitors (Supplementary Materials; Appendix 6) in combination with RT. Beddock et al[82] evaluated the combination of palbociclib and RT in patients with metastatic breast cancer. Palliative metastases were treated with standard palliative regimens to 17 vertebral body metastases, 7 peripheral bone metastases, and 1 choroidal metastasis. One patient had CTCAE grade 3 pain after radiation, and 2 patients needed to stop palbociclib during RT due to CTCAE grade 3 dermatitis and CTCAE grade 2 dysphagia. No late toxicity was described. In 3 patients with metastatic breast cancer treated with palliative lung RT (20 Gy in 5 fr) concurrently with palbociclib, 2 patients developed radiation pneumonitis refractory to corticosteroids and all developed pulmonary fibrosis.[76] Norman et al[83] demonstrated higher CTCAE grade 3 lymphopenia during cycle 1 of palbociclib in patients with breast cancer receiving 20 to 30 Gy in 5 to 10 fr RT within 1 year of palbociclib; patients who received 10 fr were more likely to have cycle 1 interrupted than those receiving shorter radiation courses.

A single-center retrospective study[84] was published on the use of concomitant palbociclib (50%), ribociclib (33%), and abemaciclib (17%) with multisite palliative RT in patients with metastatic breast cancer. RT was mostly well tolerated, with 1 patient who received 30 Gy in 10 fr to the pelvis developing a CTCAE grade 3 ileitis requiring hospitalization. The patient subsequently recovered. Two other cases of CTCAE grade 3 colitis were reported with concomitant palbociclib and 30 Gy in 10 fr to the pelvis.[85,86] Interestingly, Lee et al[87] reported that due to higher surviving crypts in the small intestine, a protective GI effect of CDK4/6 inhibitors was found when delivered before a single fr of RT compared to fractionated RT, which led to an increased risk of GI toxicity.

Summary and suggested toxicity mitigation strategies

Based on the limited, largely retrospective data available, stopping CDK 4 to 6 inhibitor 3 days before and after radiation is suggested.

Immune checkpoint inhibitors: Cytotoxic T-lymphocyte-associated protein-4, PD-1, and PD-L1 inhibitors

Immune checkpoint inhibitors work to remove inhibitory signals between tumor cells and T- cells, igniting an immune response. Cytotoxic T-lymphocyte-associated protein-4 inhibitors, such as ipilimumab, are thought to act early in the immune cycle and primarily in lymph nodes. Furthermore, cytotoxic T-lymphocyte-associated protein-4 inhibitors are believed to remove immunosuppressive molecules such as T-regulatory cells.[88] The $t^1/_2$ for ipilimumab, nivolumab, and pembrolizumab is 15.4, 25, and 22 days, respectively.[9] PD-L-1 inhibitors such as durvalumab, atezolizumab, and avelumab have a $t^1/_2$ of 18, 27, and 6.1 days, respectively[9] (Supplementary Materials; Appendix 7).

Immunotherapy appears generally safe with minimal side effects reported in patients who received conventionally fractionated RT in combination with durvalumab[89] (pneumonitis), pembrolizumab,[90,91] and nivolumab[92] (pneumonitis, esophageal fistulation).

Luke et al[93] described a 10% incidence of CTACE grade 3 or more radiation-related toxicities in a phase I

study of patients who received pembrolizumab within 7 days of SBRT. Three CTCAE grade 3 pneumonitis, 2 CTCAE grade 3 colitis, and 1 CTCAE grade 3 hepatic toxicity all within the radiation field were reported. In the setting of metastatic NSCLC, a phase 1 trial[94] and PEMBRO-RT[95] suggested that combining RT with pembrolizumab was well tolerated. One patient developed a nephritis post-SBRT to a retroperitoneal lesion, which was close to the kidney, after a third course of pembrolizumab, and another patient developed a vertebral body compression fracture post spine SBRT. Ho et al[96], in a similar phase II trial, using SBRT (30 Gy in 5 fr) concomitant with pembrolizumab to treat a patient with metastatic triple negative breast cancer, reported tolerable adverse effects with no CTCAE grade 3 or higher toxicities. A recent phase 2 trial of palliative RT (30 Gy in 10 fr) to the esophagus delivered concomitantly with pembrolizumab showed 1 CTCAE grade 3 diarrhea and 1 CTCAE grade 4 enterocolitis that required discontinuation of treatment.[97]

In addition to the many retrospective studies,[98-102] 4 prospective studies evaluated palliative RT with ipilimumab and described a rate of 14% to 34% of CTACE grade 3 or higher toxicities,[103-106] similar to drug-related toxicities only in other studies. An incidence of 1% CTCAE grade 5 immune-related bowel perforation was reported in a Kwon et al[104] phase III trial that studied ipilimumab versus placebo within 2 days before RT in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy. It was not associated with patients who received pelvic RT, and toxicity rates were again all consistent with published drug-only treatment literature.[107]

In the metastatic setting, nivolumab with moderate and ultrahypofractionation appears to be safe, with less than 13% CTCAE grade 3 toxicities reported in several studies and no grade 4 to 5 toxicities.[102,108-111] With a median follow-up of 10 months, similar radiation pneumonitis rates were reported when immune checkpoint inhibitors were given within a year of palliative RT (30 Gy in 10 fr) to the thorax.[112] Interestingly, 2 cases of radiation recall pneumonitis have been reported up to 2 years after radiation with nivolumab.[113]

Summary and suggested toxicity mitigation strategies

Several studies have reported that the combination of immunotherapy and palliative/hypofractionated RT has a potentially positive synergistic effect, while also suggesting safety in this setting. Data exist suggesting the safety of stopping ipilimumab within 2 days of single fr (8Gy) RT to the bone. However, caution should be considered for other immunotherapy agents that are less well described, with particular attention recommended when considering the RT field of treatment (eg, lungs, abdomen).

HER2 target therapies: Trastuzumab and pertuzumab

Trastuzumab is a humanized recombinant monoclonal antibody binding the extracellular domain of HER2 receptors that are currently used with breast cancer. Pertuzumab is a recombinant humanized Immunoglobulin G antibody that blocks dimerization receptors and thereby HER2-dependent signaling pathways.[114] Estimated half-life is 28[113] and 18 days,[9] respectively.

As the first anti-HER2 molecule used in clinical practice, much data exist on the safety and toxicity of combining trastuzumab and conventional RT, specifically with breast[115-121] and esophagus.[122,123] Hypofractionation up to 42.4 Gy in 16 fr appears safe based on retrospective study.[124] To the best of our knowledge, there are no current data describing the combination of ultrahypofractionated breast RT with trastuzumab.

One case report[125] in the literature described a CTCAE grade 3 radiation enteritis after palliative moderately fractionated radiation with HER2 target therapy in a patient with metastatic breast cancer who was treated to the fifth lumbar vertebra and left hip. The patient developed greater than expected radiation gastroenteritis after 24 Gy in a 30 Gy plan. Another grade 3 gastroenteritis was described 1 month after 50.4 Gy in 28 fractions to a pancreas metastasis from a breast cancer.[125] Only 1 retrospective study evaluated trastuzumab plus pertuzumab with concomitant RT in metastatic breast cancer.[115] With palliative dose, 1 patient treated with 15 Gy in 5 fr to thoracic vertebra level 8 to 11 developed an asymptomatic decrease of left ventricular ejection fraction (below 50%) 8 months after RT (heart mean dose 4.46 Gy). This patient also had other risk factors: previous right-side breast/locoregional RT and they had received epirubicin. The HER2 regimen was stopped for 3 months, and the patient recovered. Other CTCAE grade 3 toxicities described in this paper where when higher conventionally fractionated doses were used (Supplementary Materials; Appendix 9).

Summary and suggested toxicity mitigation strategies

Trastuzumab may be delivered concurrently with radiation, with attention to heart dosimetry suggested. Pertuzumab is often used in combination with trastuzumab, and toxicity rate associated with radiation appear similar, but limited data exist.

Lapatinib

Lapatinib is a TKI that acts as a reversible inhibitor of the phosphorylation in the intracellular domain of the

HER1/HER2 and downstream receptors. It has a $t^1/_2$ of 24 hours.[9]

There are little data reporting toxicity outcomes when combining lapatinib with hypofractionated RT. A number of phase I and II studies using conventionally fractionated RT have most commonly reported dermatologic side effects only.[126-129]

Summary and suggested toxicity mitigation strategies

To the best of our knowledge, there are no data reporting lapatinib being used in combination with hypofractionated or palliative RT, and the use of the half-life of lapatinib is suggested until further data become available to mitigate potential side effects.

T-DM1

Trastuzumab emtansine (T-DM1) is a systemic therapy combining trastuzumab with mertansine that inhibits mitosis, with a half-life of 3.5 days,[9] most commonly used in HER2-positive breast cancer.

The majority of existing data are from when T-DM1 is combined with conventionally fractionated RT.[130-134] Side effects reported in this setting are minimal (radiation dermatitis, pneumonitis, and cardiac toxicities), and safety has been reported when administrated with concurrent RT in a recent systemic review.[135]

Summary and suggested toxicity mitigation strategies

Limited data exist for patients receiving palliative RT concurrently with T-DM1. Combination with conventional fractionation appears safe.

Discussion

Limited data exist assessing the safety and tolerability of combined palliative RT regimens in patients with metastatic disease receiving systemic, immune, and targeted therapies, as summarized in this review. There is also a lack of reported RT data, with very few studies detailing normal tissue dose volume histograms, planning parameters, and delivered dose, limiting more sensitive analysis. Furthermore, much of the published data used a combination of systemic therapies (vs mono-therapy), making it difficult to establish the cause and effect of therapies alone or in combination. Reporting bias is reflected by only published data being available for review, and real-time clinical data may not be reflected accurately.

Deciding on an appropriate washout period requires consultation with the multidisciplinary team, including medical oncology, to determine the risk/benefit ratio in continuing systemic therapies, especially in the setting of urgent or emergency palliative RT and patients with oligo-progressive disease on continuous systemic therapy.

Conclusions

There is an urgent need for further prospective data reporting the safety, efficacy, and ideal timing of concurrent systemic, targeted, and immune therapies with moderate and ultrahypofractionated RT in the palliative setting.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101022.

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