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Safety and Tolerability of Metastasis Directed Radiotherapy in the Era of Evolving Systemic, Immune and Targeted Therapies

Short title: Metastasis Radiotherapy and Systemic Therapy

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Purpose

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

Methods and materials

A comprehensive search was performed between 1946 to August 2021 using pre-determined keywords describing the use of non-central nervous system palliative RT with commonly used targeted systemic therapies on Pubmed®

and Medline® databases. A total of 1022 articles were screened, 130 met pre-specified criteria to be included in this review.

Results

BRAF and MEK inhibitors are reported to be toxic when given concurrently with RT and suspension 3 days and 1-2 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/hypo-fractionated RT setting, suspending cetuximab during radiation week, Erlotinib/Gefitinib 1-2 days and Osimertinib ≥ 2 days pre and post RT is suggested. VEGF inhibitors such as bevacizumab reported substantial toxicities, suggestion is to suspend 4 weeks before and after radiation. Less data exists on sorafenib and sunitinib; 5 to 10 days suspension before and after RT should be considered. As a precaution, until further data is available, for CDK4-6 inhibitors, consideration to suspending of treatment 1-2 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.

Conclusion

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

Introduction

The use of cancer directed therapy is rapidly advancing, in the era of individualised patient directed care, and 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 anti-tumour immune response and in an effort to avoid interruptions of systemic treatment in patients metastatic disease[1–3].

Limited prospective safety and tolerability data exists when combining systemic therapies and RT in the metastatic setting. The aim of this review is to describe up to date published data on the safety and tolerability of metastasis directed hypo-fractionated RT when combined with newer systemic, immune, and targeted therapies, and 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 restricted to English language and human subjects, with subject-specific keywords developed as per authors' consensus (XX, XX). Controlled vocabulary terms were used when available referring to palliative RT, SBRT, bone metastases, targeted therapy, check-point inhibitor, BRAF inhibitor, MEK inhibitor, immunotherapy, PD-1 inhibitor, PDL-1 inhibitor, tyrosine kinase inhibitor and CDK4-6 inhibitor (Appendix 1 for completed list). The most recent search was performed May, 17th, 2022. Of 1029 screened articles, only prospective, retrospective studies, 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 non-metastatic RT combined with contemporary systemic therapies were 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 systems was delivered or radionuclide therapy was used and if safety data was not available. A further eight publications were added from the authors own library. A total of 130 publications were selected.

Publications including typically used palliative and/or metastatic directed RT fractionation regimens - moderate (defined as >2.2 Gray (Gy) per fraction (fr)) and ultrahypofactionation (defined as ≥5 Gy per fr (≤10 fr))[4] (with SBRT specified as ≤6 fr) were included in this analysis. These two 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 the above 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.

Radiotherapy and BRAF/MEK inhibitor agents

Vemurafenib and dabrafenib are the two 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 ½ of 57 hours[9] (range 30 to 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 Common Terminology Criteria for Adverse Events (CTCAE) grade 3 higher toxicity reported, and subsequently 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, when treating with 30 Gy in 10 fr, the estimated dose received by the skin was 23-31 Gy, resulting in a grade 3 dermatitis[30].

Non-dermatologic toxicities are less commonly reported in the literature (Appendix 2). Anker et al. reported a CTCAE grade 5 hepatic hemorrhage which occurred following 20 Gy in 5 fr using parallel opposed beam

radiation delivered to T10 toL1 vertebral body[15]. 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). Underling liver function was not reported, but additional data suggests avoiding direct liver irradiation when patients on BRAF inhibitors present with a Child-Pugh B7 and higher score[31]. A CTCAE grade 5 toxicity, reported by Baroudjia et al[11], resulted in a hemothorax one 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 reported only 2 patients (2%) with grade 3 oesophagitis with parenteral nutrition needs in their series on spine irradiation with patient with melanoma[16].

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 ½ of 4-5 hours[9]. Little information on the use as a monotherapy therefore 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 3-4 increased liver enzymes (12% vs 7%) and increased bilirubin (5% vs 0%), with no treatment related deaths occurred. However, hepatotoxicity is not a common side effect of trametinib, and 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 3D conformal RT to the lumbar spine and right ilium/L1 vertebra respectively, without any significant gastrointestinal toxicities reported by 12 months.

Summary and Suggested Toxicity Mitigation Strategies

Guidelines from the Eastern Cooperative Oncology Group (ECOG) and based on data outlined above, suspension of BRAF inhibitors 3 days before and after radiation[29] should be considered mainly to avoid skin toxicity. There is insufficient published data to provide a recommendation for MEK-inhibitors. Based on trametinib's t ½, 1-2 days pre and post RT might be sufficient.

Radiotherapy and EGFR/ALK inhibitor agents

Commonly used epidermal growth factor receptor (EGFR) inhibitors include cetuximab, erlotinib, gefitinib and osimertinib, with t ½ of 112, 36.2, 48 and 48 hours respectively[9]. Cetuximab is a monoclonal antibody targeting EGFR, whereas the other agents are receptor tyrosine kinase inhibitors (TKIs). Crizotinib is an anaplastic lymphoma kinase (ALK) inhibitors with t ½ of 42 hours[9]. ALK 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 Appendix 3.

There is a lack of data reporting the use of cetuximab combined with hypo-fractionated 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%-36% risk of CTCAE grade 3 or higher skin reaction, which is significantly increased with cetuximab compared to cisplatin[37–40]. In the palliative setting, only one case has reported a grade 3 oesophagitis when 5-FU/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 three 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 two phase 2 studies without major safety

concerns[46,47], and with conventionally fractionated RT to the rectum with a 5-38% rate of CTCAE grade 3-4 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, oesophagitis 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 gastro-intestinal cancers with concurrent erlotinib or crizotinib using SBRT and hypofractionated palliative RT, no CTCAE grade 3 or higher toxicity was reported. In the multi-institutional phase II study written by Gomez et al.[1], treating patients with oligometastatic NSCLC without progression after front-line systemic therapy, two patients received SBRT concurrently with crizotinib, reported toxicities were similar to patients who did not receive concomitant therapy. Gefitinib has also been 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. the safety of palliative hypofractionated thorax RT (30 Gy in 10 fr) with concurrent Erlotinib was demonstrated with only one CTCAE grade 3 nausea and one CTACE grade 4 dermatitis reported[65]. However, a Chinese study published a high rate of CTCAE grade 3 or higher radiation pneumonitis (54%), including one 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 hypo-fractionated RT, due to the long t ½ and paucity of toxicity data, omitting it during the week of radiation treatment is suggest. Erlotinib and gefitinib have been reported as safe with conventionally fractionated RT, but in absence of supportive data in the setting of palliative/metastasis directed RT, a washout period of 1-2 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 patient with interstitial pneumonitis.

VEGF inhibitor agents

Bevacizumab is a humanized monoclonal antibody that binds and neutralizes vascular endothelial growth factor VEFG-A with a t ½ of 20 days[9]. It is most commonly used in the management of gynecological, colorectal and hepatocellular malignancies (Appendix 4).

Bleeding after surgery in patients receiving bevacizumab have been commonly reported. A meta-analysis[66] described the incidence of gastro-intestinal perforation of 1% with 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 multi-receptor TKIs targeting, among others, the kinase c-raf, VEGFfr 2/3 and PDGF-alpha, with a t ½ of 25 to 48 hours and 40 to 60 hours respectively[9]. These agents are mostly used in hepatocellular carcinoma, renal cell carcinoma, gastrointestinal stromal tumor and thyroid carcinoma Appendix 4.

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 prior to radiation and re-started 3 days post. Murray et al[69] reported severe toxicities with concurrent sorafenib and palliative radiation (30 Gy in 10 fr), as one CTCAE grade 3 oesophagitis, one CTCAE grade 3 transaminase elevation and one 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 gastrointestinal bleeding.

A phase II trial[72] published important gastro-intestinal 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 one CTCAE grade 3 bleeds and one CTCAE grade 5 gastrointestinal hemorrhage, that was considered likely related to sunitinib rather than RT.

Summary and Suggested Toxicity Mitigation Strategies

Combining VEGF inhibitors agents with any fractionation schedule of radiation appears unsafe. Bevacizumab should be stopped at least 4 weeks prior to 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 gastrointestinal 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 ½ of 29 hours[9]. Ribociclib and abemaciclib are CDK 4-6 inhibitors with t ½ of 30 to 55 hours and 18.3 hours[9].

Few retrospective data[74–81] exist on the used of CDK4/6 inhibitors (Appendix 5) in combination with RT. Beddock et al.[82] evaluate the combination of palbociclib and RT in patients with metastatic breast cancer. Palliative metastases were treated with standard palliative regimens to 17 vertebral body metastasis, 7 peripheral bone metastasis and 1 choroidal metastasis. One patient had CTCAE grade 3 pain after radiation, 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 three patients with metastatic breast cancer treated with palliative lung RT (20 Gy in 5 fr) concurrently with palbociclib, two patients developed radiation pneumonitis refractory to corticosteroids and all developed pulmonary fibrosis[76]. Norman et al. demonstrate higher CTCAE grade 3 lymphopenia during cycle 1 of palbociclib in patients with breast cancer receiving 20-30 Gy in 5-10 fr RT within 1 year of palpociclib; patients who received 10 fr were more likely to have cycle one interrupted than those receiving shorter radiation courses[83].

A single-center retrospective study[84] was published on the use of concomitant palbociclib (50%), ribociclib (33%) and abemaciclib (17%) with multi-site palliative RT in patients with metastatic breast cancer. RT was mostly well tolerated, with one patient who received30 Gy in 10 fr to the pelvis developing a CTCAE grade 3 ileitis requiring hospitalisation. The patient subsequently recovered. Two other CTCAE grade 3 colitis were reported with

concomitant palbociclib and 30 Gy in 10 fr to the pelvis[85,86]. Interestingly, Lee et al. reported that due to higher surviving crypts in the small intestine, a protective GI effect of CDK4/6 inhibitors was found when delivered prior to a single fr of RT compare to fractionated RT which led to an increased risk of GI toxicity[87].

Summary and Suggested Toxicity Mitigation Strategies

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

Immune checkpoint inhibitors - CTLA-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 (CTLA-4) inhibitors, such as ipilimumab are thought to act early in the immune cycle and primarily in lymph nodes. Furthermore, CTLA-4 inhibitors are believed to remove immunosuppressive molecules such as T-Regulatory cells[88]. The t ½ 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 ½ of 18, 27 and 6.1 days respectively[9] (Appendix 6).

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, oesophageal 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, two CTCAE grade 3 colitis and one 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.[92] 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, tolerable adverse effects were

reported 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 one CTCAE grade 3 diarrhea and one CTCAE grade 4 enterocolitis that required discontinuation treatment[96].

In addition to the many retrospective studies[97–101], four prospective studies evaluated palliative RT with ipilimumab and described a rate of14-34% of CTACE grade 3 or higher toxicities[102–105], similar to drug-related toxicities only in other studies. An incidence of1% CTCAE grade 5 immune-related bowel perforation was reported in Kwon et al phase III trial[103] that studied ipilimumab versus placebo within 2 days prior to 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 toxicities rates are again all consistent with published drug-only treatment literature[106].

In the metastatic setting, nivolumab with moderate and ultra-hypofractionation appear to be safe with less than 13% CTCAE grade 3 toxicities reported in several studies, and no grade 4-5 toxicities[101,107–110]. 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[111]. Interestingly, two cases of radiation recall pneumonitis have been reported up to 2 years after radiation with nivolumab[112].

Summary and Suggested Toxicity Mitigation Strategies

Several studies have reported that the combination of immunotherapy and palliative/hypo-fractionated RT have a potentially positive synergistic effects, while also suggesting safety in this setting. Data exists 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 (e.g. lungs, abdomen).

HER2 target therapies

Trastuzumab and pertuzumab

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

As the first anti-HER2 molecule used in clinical practice, much data exists on the safety and toxicity of combining trastuzumab and conventional RT, specifically with breast[114–120] and esophagus[121,122]. Hypofractionation up to 42,4 Gy in16 fr appears safe based on retrospective study[123]. To the best of our knowledge, there is no current data describing the combination of for ultra-hypofractionated breast RT with trastuzumab.

One case report[124] 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 one month after 50.4 Gy in 28 fractions to a pancreas metastasis from a breast cancer[124]. Only one retrospective study evaluate trastuzumab plus pertuzumab with concomitant RT in metastatic breast cancer[114]. With palliative dose, one patient treated with 15 Gy in 5 fr to thoracic vertebra level 8-11 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 had received epirubicine. 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. (Appendix 7)

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 exists.

Lapatinib

Lapatinib is a tyrosine kinase inhibitor that acts as a reversible inhibitor of the phosphorylation in the intracellular domain of the HER1/HER2 and downstream receptors. It has a t ½ of 24 hours[9].

There is 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 dermatological side-effect onlys[125–128].

Summary and Suggested Toxicity Mitigation Strategies

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

T-DM1

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 HER-2 positive breast cancer.

The majority of existing data is when T-DM1 is combined with conventionally fractionated RT [129–133]. 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[134].

Summary and Suggested Toxicity Mitigation Strategies

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

Discussion

Limited data exists assessing the safety and tolerability of combined palliative RT regimens in patients with metastatic disease receiving systemic, immune and targeted therapies, as summarised in this review. There is also a lack of reported radiation therapy 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 (versus mono-therapy), making it difficult to establish the cause and effect of therapies alone or combination. Reporting bias is reflected by only published data being available for review with, real-time clinical data may not be reflected accurately.

Deciding on an appropriate washout period requires consultation with the multi-disciplinary 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.

Conclusion

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 ultra-hypo-fractionated RT in the palliative setting.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1: Summary of Suggested Approaches

Agents	Drug	Suggestions
BRAF and MEK inhibitor	Vemurafenib and Dabrafenib	Suspend 3 days before and after RT.
	Trametinib	Suspend 1-2 days before and after RT.
EGFR and ALK inhibitor	Cetuximab	Suspend the week of radiation if SBRT.
	Erlotinib and Gefetinib	Suspend 1-2 days before and after RT.
	Crizotinib and Osimertinib	Suspend ≥2 days before and after RT.
VEGF inhibitor	Bevacizumab	Suspend 4 weeks before and after RT.
	Sorafenib and Sunitinib	Suspend 5-10 days before and after RT.
CDK 4-6 inhibitor	Palbociclib and Ribociclib	Suspend 3 days before and after RT.
Immunotherapy	Ipilimumab	Suspend 2 days before and after RT if 8 Gy in single fraction to bone
	Other	Insufficient data to recommend with moderate and ultrafractionation RT, caution suggested on an individual basis.
HER2 target therapy	Trastuzumab and Pertuzumab	Generally safe to use concomitantly with RT.
	Lapatinib	Insufficient data to recommend with moderate and ultrafractionation RT, caution suggested on an individual basis.
	T-DM1	Insufficient data to recommend with moderate and ultrafractionation RT, caution suggested on an individual basis.

RT= radiation therapy