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ORIGINAL ARTICLE

Safety assessment of anticancer drugs in association with radiotherapy in metastatic malignant melanoma: a real-life report

Radiation/systemic drug combo in metastatic melanoma

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Abstract

Purpose To assess the safety of the association of radiotherapy (RT) and systemic treatments for patients with metastatic malignant melanoma (mMM).

Methods A retrospective analysis included consecutive patients treated with palliative RT, and at least one line of systemic therapy for mMM between 2001 and 2016. Treatments were defined as sequential or concomitant when RT and the systemic drug were administered, respectively, at more or less than five half-lives from each other.

Results 92 patients were included. They had 110 palliative RT treatments. RT was delivered with a "conventional" chemotherapy (mainly fotemustine and/or dacarbazine) and a "modern" systemic therapy (BRAF inhibitors, association of BRAF and MEK inhibitors, immunotherapy), respectively, in 88 (80%) and 22 (20%) cases. Systemic treatments and RT were mainly concurrently performed ($n=61$, 55.5%). Regarding acute grade ≥ 3 toxicity, no difference was reported between sequential and concomitant groups either in the whole cohort ($p=1$) or in the subgroup of patients receiving "modern" systemic therapies ($p=1$). Acute and late grade ≥ 3 toxicities only occurred with vemurafenib. BRAF inhibitors and RT produced more severe infield adverse events than other associations ($p=0.001$) with two deaths.

Conclusion In our series, compared to sequential administration, concomitant association of systemic anticancer drugs and palliative RT did not increase toxicity in mMM patients. BRAF inhibitors and RT produced severe infield toxicities. Prospective studies are needed to better characterize the toxicity of each association.

Keywords Melanoma · Radiation therapy · Systemic drugs · Toxicity

Introduction

The incidence of malignant melanoma (MM) has been increasing in Europe for the last decade [1]. Local stage MM have a good prognosis when a large local surgical resection is achieved [2]. However, metastases are common, either at diagnosis or during the follow-up of an initially localized MM. The treatment of metastatic MM (mMM) is based on systemic anticancer therapies [3]. For the last 10 years, mMM management has largely evolved from the era of "conventional" chemotherapies (mainly dacarbazine and fotemustine) to the age of targeted therapies and immunomodulation. These "modern" therapies

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improved progression-free-survival (PFS) and overall survival (OS) [3]. Increasing knowledge on tumor biology has allowed the development of genomic adapted therapies. Thus, the BRAF V600 mutation—found in almost 45% of mMM patients [1]—indicates a first-line therapy based on the association of anti-BRAF and anti-MEK-targeted therapies (vemurafenib or dabrafenib and cobimetinib or trametinib) [4–6]. Moreover, immunotherapy has recently been successfully developed in mMM. Monoclonal antibodies such as nivolumab [7, 8], pembrolizumab [9] or ipilimumab [10, 11] have been designed to block CTLA4, PD1 T-lymphocytes receptors and PDL1 tumor receptors and reactivate the patient's anticancer immunity.

While the place of radiation therapy (RT) has been studied for locally advanced MM [12–14], RT is mostly indicated at the metastatic setting for symptom palliation [1]. Thus, the maintenance of systemic anticancer treatment during palliative RT is frequently discussed by oncologists who remain divided between the need to maintain pressure on tumor and the risks of increased infield side effects. Recommendations about the association of these new treatments (targeted therapies, immune therapies) with RT have been published. Some were based on the precautionary principle and used pharmacokinetic definitions [15], whereas others relied on large literature analysis [16].

The present study aims at assessing the safety of the association of mMM systemic drugs and RT, based on a pharmacokinetic definition of sequential and concomitant administrations.

Materials and methods

A retrospective study was conducted at Lucien Neuwirth Comprehensive Cancer Care Center (France) and Saint-Etienne University Hospital (France). The institutional review board approved the study which was conducted in compliance with the Helsinki declaration.

Patient population

All consecutive patients aged 18 and over, diagnosed with mMM and treated at least once with anticancer drugs and RT between 2001 and 2016 at the Lucien Neuwirth Comprehensive Cancer Care Center were retrospectively included. Patients who did not receive any systemic drug were excluded. Patients' characteristics, treatment (RT and chemotherapy) characteristics, toxicity of each treatment and outcomes were retrospectively reviewed in medical records.

Table 1 Pharmacokinetic data about systemic treatments of metastatic malignant melanoma administered in association with radiation therapy [18]

Systemic treatment	$T_{1/2}$	5 $T_{1/2}$
Conventional chemotherapies		
Dacarbazine	35 min	2.9 h
Fotemustine	0.5–2 h	2.5–10 h
Platinum salts	5 days	25 days
Vindesine	1 day	5 days
Temozolomide	1.8 h	9 h
Paclitaxel	23.7 h	4.9 days
Immunotherapy		
Ipilimumab	15.4 days	2.6 months
Nivolumab	17–27.5 days	2.8–4.6 months
Pembrolizumab	26 days	4.3 months
Targeted therapy		
Vemurafenib	51.6 h	10.8 days
Cobimetinib	43.6 h	9.1 days

$T_{1/2}$ half-life of systemic treatment

Systemic drugs

The systemic treatments were conventional chemotherapies (dacarbazine, fotemustine, vindesine, platinum salts, paclitaxel, temozolomide), targeted therapies (vemurafenib, cobimetinib) and immune therapies (ipilimumab, nivolumab, pembrolizumab).

Concomitant and sequential RT-systemic therapy association

The systemic treatment which was taken into account, was the nearest to the RT session (either before or after). In the present study, concepts of concurrent or sequential RT-systemic therapy association were based on the pharmacokinetic definition of the half-life: 97% of a drug are eliminated after 5 half-lives and are considered inactive for the human body [17]. Thus, when the time between the last administration of the systemic treatment and the beginning of RT or, between the end of RT and the administration of the systemic drug was upper than 5 half-lives of the considered drug, the association was sequential. In all other cases (i.e., time between the last administration of the systemic treatment and the beginning of RT or between the end of RT and the new administration of the systemic drug being less than or equal to 5 half-lives), the association was concurrent. In the concomitant treatment group, toxicities were reported separately in two subgroups. First, when the systemic treatment was administered at a time interval equal to or less than one-half-life from RT session. Second, when the systemic

treatment was administered at a time interval of more than one half-life, and up to five half-lives from RT session. Half-life systemic treatments are summarized in Table 1 [18].

Safety outcomes

Acute and late toxicities were retrospectively assessed in the patient's medical record. Acute toxicities were defined by adverse events occurring, respectively, within 3 months after RT completion. Late toxicities occurred later. Toxicities were graded based on the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0) [19]. The toxicity assessment of each systemic treatment was achieved by one author only. Another author assessed toxicity related to RT. Data were then cross-checked. If authors disagreed about grading toxicity, a third author ascertained the toxicity. The most severe toxicities, which are infield of RT ("infield toxicities"), were particularly cautiously assessed.

Statistical analysis

Follow-up was defined by time interval between the end of the first RT treatment and the date of the last visit. Median values were given with their ranges. Fisher's exact test was performed between sequential and concurrent administration group for the whole cohort and for the subgroup of "modern" systemic treatments to assess differences regarding severe (i.e., grade ≥ 3) acute and late toxicities.

Results

Patients' and tumor characteristics

Ninety-two patients were included. They had 110 RT treatments since some patients experienced multiple RT treatments. Only palliative irradiations were performed. Sequential and concomitant administration group, respectively, included 49 (44.5%) and 61 (55.5%) RT treatments. In the concomitant group, 56 RT treatments were delivered at ≤ 1 half-life of the considered systemic drug and 5 RT treatments performed between 1 and 5 half-lives of the considered systemic drug. Median age for the whole cohort was 61.4 years (IQR 53.1–68.4). Most patients were in good condition. Their performance status was 0–1 for 90% of RT treatments. The most frequent histology of primary melanoma was spreading superficial melanoma (49.1%). Primary melanoma was mainly located on limbs (35.5%), trunk (23.6%) and head and neck (19.1%). Breslow Index was mainly between 2.01 and 4 mm (28.2%). Metastases were mainly located in lymph nodes (46.3%), skin (43.6%), lung (29.1%), brain (22.7%) and liver (19.1%). Before radiotherapy, 70 patients (76%) experienced a surgery on the primary melanoma. Regarding lymph node management, the surgery initially included an extensive lymph node dissection in seven patients (7.6%). The surgery included the analysis of the sentinel node in 50 patients (54.3%). An extensive lymph node dissection was performed in 23 patients (46%) after sentinel node analysis. Most RT treatments (60%) were performed on patients who had previously experienced at least 1 line of systemic therapy. However, patients experiencing targeted therapies (i.e., tyrosine kinase inhibitors) mainly had RT in combination with the first-line treatment (83%). Patient's and tumor characteristics are detailed in Table 2.

Radiation therapy characteristics

Radiotherapy was mainly delivered using a tridimensional conformal technique ($n = 103$, 93.6%). Seven RT treatments (6.4%) were delivered with stereotactic body radiation therapy (SBRT). SBRT was always performed on brain metastases. 30 Gy (IQR 30–36 Gy) in ten fractions (IQR 8–10) were the median dose and fractions. Brain was the most frequently irradiated site whatever the treatment arm with, respectively, 17 (34.7%) and 36 (59%) brain RT in sequential and concomitant arms. Other treated locations were mainly bone ($n = 23$, 20.9%) and cutaneous ($n = 22$, 20%). RT characteristics are summarized in Table 3.

Systemic drug characteristics

Regarding the whole cohort, respectively, 88 (80.1%), 12 (10.9%) and 10 (9%) RT treatments were delivered in addition to a conventional chemotherapy (38 sequentially and 50 concomitantly), a targeted therapy (7 sequentially and 5 concomitantly) and immunotherapy (4 sequentially and 6 concomitantly). The most frequently administered conventional chemotherapy was fotemustine (52.3%): 21 sequentially and 23 concomitantly. Vemurafenib was the most frequent targeted therapy (91.7%): 6 sequential and 5 concomitant administrations. Finally, ipilimumab was the most commonly used immunotherapy (60%) with 3 concomitant and 3 sequential administrations. Systemic drug characteristics are summarized in Table 4.

Survival and local outcomes

The median follow-up for the entire cohort was 4.2 months (IQR 1.7–9.4 months). At the date of the analysis, 78 patients (84.8%) had died. All deaths caused by mMM, except two which were related to complications due to radiation. After RT, no abscopal effect (tumor response out of the field of RT, consecutively to RT) was reported. Infield local control was 60% but symptom palliation was achieved after 80% of RT treatments.

Table 2 Patients' and tumor characteristics

Characteristics	Sequential administration (> 5 $T_{1/2}$)	Concomitant administration (≤ 5 $T_{1/2}$)		All treatment courses
		≤ 1 $T_{1/2}$	]1–5] $T_{1/2}$	
Number of patients	49	56	5	110
Median age (IQR) (years)	62.7 (53.4–73)	61.4 (54.6–66.9)	46.3 (37–61.3)	61.4 (53.1–68.4)
Gender				
Male	27	35	4	66
Female	22	21	1	44
Performance status				
0–1	44	50	5	99
2	4	4	0	8
3	0	1	0	1
Missing data	1	1	0	2
Mean body mass index (range) (kg/m^2)	25.4 (19.5–39.8)	27.5 (16.5–50.9)	25.5 (23.7–28)	26.1 (16.5–50.9)
Tumor histology				
Spreading superficial melanoma	29	25	0	54
Acral lentiginous melanoma	9	7	0	16
Nodular melanoma	3	5	2	10
Lentigo malignant melanoma	2	3	0	5
Mucosal melanoma	2	3	0	5
Other	2	2	2	6
Missing data	2	11	1	14
Melanoma location				
Limb	20	17	2	39
Trunk	14	10	2	26
Head and neck	8	13	0	21
Acral	4	2	0	6
Nail	0	3	0	3
Other	1	2	0	3
No primitive tumor	2	8	1	11
Missing data	0	1	0	1
Breslow (mm)				
≤ 1 mm	5	5	0	10
[1.01–2]	11	10	0	21
[2.01–4]	15	15	1	31
> 4	9	8	3	20
Missing data	9	18	1	28
Metastases location[a]				
Liver	7	12	2	21
Lung	9	20	3	32
Bone	4	8	–	12
Brain	9	16	–	25
Skin	23	22	3	48
Lymph nodes	20	28	3	51
Adrenal gland	–	3	–	3
Spleen	1	–	–	1
Systemic anticancer therapies				
Conventional chemotherapies				
First line	13	19	–	32
Second line	20	24	1	45
Third line	4	5	–	9

Table 2 (continued)

Characteristics	Sequential administration (> 5 $T_{1/2}$)	Concomitant administration (≤ 5 $T_{1/2}$)		All treatment courses
		≤ 1 $T_{1/2}$	]1–5] $T_{1/2}$	
Fourth line	–	1	–	1
Fifth line	1	–	–	1
Immune therapies				
First line	1	–	1	2
Second line	1	2	1	4
Third line	2	–	2	4
Fourth line	–	–	–	–
Fifth line	–	–	–	–
Targeted therapies				
First line	5	–	5	10
Second line	–	–	–	–
Third line	–	–	–	–
Fourth line	–	–	–	–
Fifth line	2	–	–	2

$T_{1/2}$ half-life of systemic drug, *n* number of patients, *IQR* interquartile, *Gy* gray

[a]At the time, the metastatic setting was diagnosed

Toxicities

Acute toxicities

In the sequential administration group, three acute all-grade infield toxicities (6.1%) were reported, among which one grade 5. Grade 5 toxicity was an acute brain hemorrhage leading to coma and death. The patient experienced a brain SBRT delivering 24 Gy in three fractions. The first fraction was performed 2 weeks after the last administration of vemurafenib. For the concomitant group, eight acute all-grade infield toxicities (14.3%) occurred in the "≤ 1 half-life" subgroup, whereas no toxicity was reported in the "1–5 half-lives" subgroup. Among the eight acute infields, all grade toxicities reported, one grade 3 and one grade 5 acute toxicities occurred. Grade 3 toxicity was an intracranial hypertension syndrome occurring during a whole brain RT (37.5 Gy in 15 fractions) with concurrent vemurafenib. Grade 5 toxicity was a brain herniation leading to death immediately after a whole brain RT (30 Gy in 10 fractions) with concurrent vemurafenib. Descriptive data about acute infield toxicities are reported in Table 5. No difference was found between sequential and concomitant administration groups for occurrence of acute grade ≥ 3 infield toxicities (OR = 1.62 [IC 95% 0.1–97.9]; $p = 1$). Moreover, no difference was shown for the occurrence of acute grade ≥ 3 infield toxicities between sequential and concomitant administration arms considering the subgroup of 22 patients receiving "modern" therapies like targeted therapies or immunotherapies (OR = 2.1 [IC 95% 0.1–143.8]; $p = 1$). When targeted therapies were separately analyzed (12 patients), no difference was found between the concomitant or sequential groups regarding infield acute grade ≥ 3 toxicity ($p = 0.52$). The incidences of infield grade ≥ 3 acute toxicities were then compared: conventional chemotherapy versus targeted therapies versus immune therapies. It revealed the incidence significantly increased in targeted therapy (i.e., BRAF inhibitors) patients ($p < 0.001$).

Late toxicities

Considering the whole cohort, only 1 grade ≥ 3 infield late toxicity was reported. It was a grade 4 toxicity corresponding to the occurrence of an inguinal cutaneous-digestive fistula following a left inguinal RT. Radiation dose was 20 Gy in five fractions. At the beginning of RT, vemurafenib had been stopped for 2 months. No difference between sequential and concomitant groups in the whole cohort was highlighted for grade ≥ 3 infield late toxicity ($p = 0.4$).

Discussion

The present retrospective cohort reports a mono-institutional experience on the safe association of mMM systemic drugs with RT. Considering sequential or concomitant administration, no difference was found regarding acute grade ≥ 3 infield toxicities, whether in the whole cohort or in the subgroup of "modern" systemic therapies (i.e., targeted therapies or immunotherapy). However, all acute and late grade ≥ 3 toxicities occurred with vemurafenib, suggesting that irradiation should be cautiously performed in patients

Table 3 Radiation therapy characteristics

Treatment characteristics	Sequential administration	Concomitant administration	
		$\leq 1\ T_{1/2}$	]1–5] $T_{1/2}$
Number of patients	49	56	5
Median dose (IQR) (Gy)	30 (30–36)	30 (30–36.4)	30 (30–30)
Median number of fractions (IQR)	10 (5–10)	10 (10–10)	10 (10–10)
Radiation therapy sites			
Whole set of patients			
Brain	17	31	5
Bone	11	12	–
Vertebral	7	10	–
Pelvis	–	1	–
Limb	2	–	–
Rib	1	–	–
Right clavicle	1	1	–
Cutaneous	13	9	–
Lymph node	6	3	–
Other	2	1	–
Right maxillary sinus	1	–	–
Abdominal mass	1	1	–
Conventional chemotherapies			
Brain	12 (with 2 SBRT)	25	1
Bone	9	12	–
Vertebral	7	10	–
Pelvis	–	1	–
Limb	1	–	–
Rib	1	–	–
Right clavicle	–	1	–
Cutaneous	12	9	–
Lymph node	4	3	–
Other	1	–	–
Abdominal mass	1	–	–
Immune therapies			
Brain	1 (with 1 SBRT)	1 (with 1 SBRT)	4
Bone	1	–	–
Right clavicle	1	–	–
Lymph node	1	–	–
Other	1	1	–
Abdominal mass	–	1	–
Right maxillary sinus	1	–	–
Targeted therapies			
Brain	4 (3 SBRT)	5	–
Bone	1	–	–
Limb	1	–	–
Cutaneous	1	–	–
Lymph node	1	–	–

$T_{1/2}$ half-life of systemic drug, *n* number of patients, *IQR* interquartile, *Gy* gray, *SBRT* stereotactic body radiotherapy

experiencing BRAF inhibitors. Nevertheless, the present article features limitations. First, systemic therapies and location of radiation treatments were both highly fluctuating. This resulted in heterogeneous groups, which certainly makes firm conclusions difficult to draw. Second, the retrospective nature of the analysis was a major drawback,

Table 4 Systemic drug characteristics

Systemic drug administered	Sequential administration	Concomitant administration		Total
		$\leq 1\ T_{1/2}$	$]1–5]\ T_{1/2}$	
Conventional chemotherapy [*n* (%)]	38 (34.6)	49 (44.6)	1 (0.9)	88 (80.1)
Fotemustine	21	22	1	46
Dacarbazine	10	13	0	23
Dacarbazine + fotemustine	4	9	0	13
Carboplatin + paclitaxel	1	0	0	1
Vindesine	0	1	0	1
Vindesine + platinum salts	0	2	0	2
Temozolomide	0	1	0	1
Cisplatin	0	1	0	1
Targeted therapy [*n* (%)]	7 (6.4)	5 (4.5)	0 (0)	12 (10.9)
Vemurafenib	6	5	0	11
Vemurafenib + cobimetinib	1	0	0	1
Immunotherapy [*n* (%)]	4 (3.6)	2 (1.8)	4 (3.6)	10 (9)
Ipilimumab	3	0	3	6
Nivolumab	0	2	1	3
Pembrolizumab	1	0	0	1
Total [*n* (%)]	49 (44.6)	56 (50.9)	5 (4.5)	110 (100)

$T_{1/2}$ half-life of systemic drug, *n* number of patients

Table 5 Infield acute toxicity occurring with sequential and concomitant administration of systemic drugs with radiotherapy

Systemic drug administered	Sequential administration			Concomitant administration					
				$\leq 1\ T_{1/2}$			$]1–5]\ T_{1/2}$		
n	49			56			5		
Toxicity	All grades	Grade 3–4	Grade 5	All grades	Grade 3–4	Grade 5	All grades	Grade 3–4	Grade 5
Conventional chemotherapy	2	0	0	6	0	0	0	0	0
Fotemustine	0	0	0	0	0	0	0	0	0
Dacarbazine	2	0	0	2	0	0	0	0	0
Dacarbazine + fotemustine	0	0	0	4	0	0	0	0	0
Carboplatin + paclitaxel	0	0	0	0	0	0	0	0	0
Vindesine	0	0	0	0	0	0	0	0	0
Vindesine + platinum salts	0	0	0	0	0	0	0	0	0
Temozolomide	0	0	0	0	0	0	0	0	0
Cisplatin	0	0	0	0	0	0	0	0	0
Targeted therapy	1	0	1	2	1	1	0	0	0
Vemurafenib	1	0	1	2	1	1	0	0	0
Vemurafenib + cobimetinib	0	0	0	0	0	0	0	0	0
Immunotherapy	0	0	0	0	0	0	0	0	0
Ipilimumab	0	0	0	0	0	0	0	0	0
Nivolumab	0	0	0	0	0	0	0	0	0
Pembrolizumab	0	0	0	0	0	0	0	0	0
Total [*n* (%)]	3 (6.1)	0 (0)	1 (2.1)	8 (14.3)	1 (1.8)	1 (1.8)	0 (0)	0 (0)	0 (0)

especially because of the lack of low-grade toxicity data (grade 0–2 toxicities were not reported in patients' medical records). Regarding late toxicities, the short median follow-up (4 months) certainly made the assessment of delayed complications inaccurate. However, the overall survival of mMM patients was very limited until recently. As our study reports on outcomes collected for the last 15 years, the short follow-up directly reflected the short-term survival of most patients. Besides, in a palliative setting, the evaluation of the therapeutic index (efficacy/toxicity ratio) of RT is

more based on acute than on late toxicity. Indeed, even with patients undergoing TKI of immune therapies, the overall survival of metastatic MM is still limited, making the probability of a late toxicity low. Most of the time, late symptoms are expected to appear in the 6–24 months following RT, i.e., much longer than the patient's life expectancy. Conversely, acute toxicities can be life-threatening and ruin the quality of the end of life, which is probably the reason why the existing literature almost exclusively reported on acute toxicity. Third, the small number of patients receiving RT with a "modern" therapy limits the conclusions of this report. Indeed, 80% of the cohort received the oldest chemotherapy regimen (dacarbazine or fotemustine) that are now only performed in 3rd–4th line for companionate use. However, even near the very end of life, a palliative RT is still frequently performed [20, 21]. In this setting, the accurate evaluation of the toxicities induced by the combination RT-chemotherapy is crucial. A misperception can directly induce a major degradation of the quality of the end life or worse, the death in frail patients. Still, to our best knowledge, the safety of the association of palliative RT with conventional chemotherapies (dacarbazine, fotemustine) had never been reported in mMM patients. The present results suggest that this combination is safe. Our results are in accordance with studies performed in glioblastomas patients, in whom no abnormal toxicity was reported with similar associations.

The association of systemic drugs with RT has been a daily issue for oncologists, especially since the development of "modern" systemic therapies. Historical data exploring the impact of targeted therapies or immune therapies on infield radiation-induced toxicities are rare, though. The results of numerous clinical trials have not been published yet [22]. Therefore, recommendations for the management of systemic drugs in this situation are currently based on pharmacokinetic principles which consider that 97% of the active principle of a drug is eliminated after 5 half-lives [17]. Based on this concept, Thariat et al. provided guidelines to safely perform a stereotactic body radiotherapy (SBRT) close to a systemic drug administration [15]. However, in daily routine, stopping the considered anticancer drug five half-lives before and after RT cannot systematically be observed—especially for immunotherapies whose half-lives are long (Table 1). Therefore, decisions on a case-by-case basis should often be made taking into account the medical evaluation of benefit/risk balance and literature. The safety of the association of RT and systemic therapies (such as tyrosine kinase inhibitors or mTOR inhibitors) has already been reported in renal carcinoma. The concept of the half-lives of the systemic therapy was also used. Toxicity did not increase between sequential and concurrent administrations [23]. In 2016, Anker et al. published consensus guidelines from the Eastern Cooperative Oncology Group (ECOG) for the management of BRAF inhibitors combined with RT, based on an extensive literature review [16]. Forty publications were identified. They involved 89 patients in whom an extra-cranial infield toxicity had been reported with the association RT/BRAF inhibitors. The proportion of patients with infield toxicities was not given. Therefore, a comparison with the rates of toxicities in the present study could not be performed. After an analysis of all concurrent/sequential administrations of toxic associations, Anker et al. advised to stop BRAF inhibitor ≥ 3 days before and after fractionated RT and ≥ 1 day before and after stereotactic radiosurgery. Although the large literature review performed by Anker et al. showed no significant intracranial, mucosal, hepatic or lung increased toxicities regardless of a concurrent or sequential administration of BRAF inhibitors [16], some case reports revealed severe visceral toxicities. Anorectitis were reported with RT and BRAF inhibitors' combination [24]. Concurrent vemurafenib and RT administration also caused grade 2 and 3 dermatitis [25–33]. In a large multicenter analysis, the rate of grade ≥ 2 radiodermatitis increased after a whole-brain RT combined with BRAF inhibitors (44% versus 8% without BRAF inhibitors, $p < 0.001$) [34]. So far, guidelines have not been supported by high quality historical data since they mainly consist of case reports and non-randomized early phase trials. However, prospective clinical trials including patients who could require palliative RT will certainly provide an answer in the forthcoming years (NCT02224781 and NCT02164916). Regarding intracranial toxicities, brain radionecrosis was also reported when RT was associated with vemurafenib [35]. The recent results of an open-label, single-arm, phase II, multicenter study suggested that vemurafenib could be safely sequentially associated with brain stereotactic body radiotherapy. Out of the 56 patients with brain metastases who previously received RT before vemurafenib, one experienced infield toxicity (hemorrhage). This was not statistically different from the group which never received brain RT. However; the very limited number of patients in this study is a major limitation. Furthermore, no concomitant association was performed. The literature about intracranial toxicities due to RT-BRAF inhibitors association has recently been extensively reviewed [36]. The results of seven studies were analyzed. The conclusions were limited because of the absence of control arm and the discrepancy between studies, but toxicities were frequent (0–100% of radionecrosis, 29–100% of intratumoral hemorrhage). Because of these inconclusive reports, the ECOG recommended the same attitude for intracranial and extra-cranial RT: stopping BRAF inhibitors ≥ 1 day before and after radiosurgery and ≥ 3 days before and after fractionated radiotherapy. In addition, ECOG recommended a radiation dose per fraction < 4 Gy unless SBRT was used or in patients with poor prognosis/performance status. Interestingly, the action of BRAF inhibitors could perfectly explain the occurrence of adverse

Table 6 Currently recruiting clinical trials based on the concurrent association of radiation with tyrosine kinase inhibitors or immune therapies

Nature	Identifier	Trial's name	Intervention	Primary outcome measures
Immune therapies (anti PD1, anti-CTLA4, anti-PDL1)				
Phase I, monocenter, open-label study	NCT02858869	Pembrolizumab and stereotactic radiosurgery for melanoma or non-small cell lung cancer brain metastases	Arm A: pembrolizumab, SBRT 5 × 6 Gy Arm B: pembrolizumab, SBRT 3 × 9 Gy Arm C: pembrolizumab, SBRT 1 × 12 Gy	3-Month neurological DLT
Phase I, monocenter, open-label study	NCT02716948	SRS and nivolumab in treating patients with newly diagnosed melanoma metastases in the brain or spine	SRS + nivolumab	3-Month incidence of serious adverse events (any grade)
Phase I, monocenter, open-label study	NCT02639026	Trial of hypofractionated radiotherapy in combination with MEDI4736 and tremelimumab for patients with metastatic melanoma and lung, breast and pancreatic cancers	Arm A: SRS 8 Gy/1 Fr + MEDI4736 + tremelimumab Arm B: SRS 17 Gy/1 Fr + MEDI4736 + tremelimumab	Not detailed
Phase I/II, monocenter, open-label study	NCT02407171	Evaluating the combination of MK-3475 and stereotactic body radiotherapy in patients with metastatic melanoma or NSCLC	SBRT (30 Gy/5 Fr or 30 Gy/3 Fr or 10 Gy/1 Fr) + pembrolizumab	Phase I: DLT incidence Phase II: overall response rate (time frame: up to 12 months)
Phase I/II, multicenter, open-label study	NCT03354962	Induction of immune-mediated aBscOpal Effect thrOugh STEreotactic radiation therapy in metastatic melanoma patients treated by PD-1 + CTLA-4 inhibitors (BOOSTER MELANOMA)	Arm A: nivolumab + ipilimumab Arm B: SBRT + nivolumab + ipilimumab	Phase I: DLT incidence, abscopal effect incidence Phase II: 6-month PFS
Phase II, open-label, randomized, monocenter study	NCT03646617	Ipilimumab and nivolumab with or without hypofractionated radiotherapy in patients with metastatic melanoma (RadVax)	Arm A: ipilimumab + nivolumab Arm B: SBRT (3 × 8 Gy) + ipilimumab + nivolumab	Number of adverse events (time frame: 3.5 years)
Phase II, monocenter, open-label study	NCT03050060	Image Guided hypofractionated radiation therapy, nelfinavir mesylate, pembrolizumab, nivolumab and atezolizumab in treating patients with advanced melanoma, lung, or kidney cancer	Combination of hypofractionated radiotherapy with PD1/PDL1 immune checkpoint (nivolumab or pembrolizumab) and nelfinavir mesylate (nelfinavir)	Safety, tolerability and preliminary assessment of ORR (time frame: 2 years after treatment initiation)
Phase II, monocenter, open-label study	NCT03693014	A study of several radiation doses for patients with progression on immunotherapy/checkpoint inhibitors	SBRT (27 Gy/3 Fr) on 1–3 lesions, combined with immunotherapy/checkpoint inhibitors (ipilimumab or nivolumab, pembrolizumab)	Abscopal effect: ORR in non-irradiated lesions (time frame: 24 weeks after treatment initiation)
Phase II, open-label, multicenter study	NCT02799901	Nivolumab plus radiotherapy in advanced melanoma (NIRVANA)	Nivolumab + SBRT (3 × 6 Gy on one metastasis for each tumor site, defined as skin/muscle, thoracic, abdomen, bone, other)	Overall survival (time frame: 1 year)
Phase II, open-label, randomized, multicenter study	NCT03511391	CHEckpoint Inhibition in Combination With an Immunoboost of External Body Radiotherapy in Solid Tumors (CHEERS)	Arm A: pembrolizumab or nivolumab Arm B: SBRT (3 × 8 Gy on a maximum of 3 sites) + pembrolizumab or nivolumab	Progression-free survival (time frame: 15 months)

Table 6 (continued)

Nature	Identifier	Trial's name	Intervention	Primary outcome measures
Tyrosine kinase inhibitors				
Phase I/II, multicenter, open-label study	NCT02392871	Radiotherapy and Combi in metastatic melanoma (CombiRT)	Palliative radiotherapy (up to three areas treated at the same time) in combination with dabrafenib and trametinib	Toxicity assessment, by measuring adverse events and radiotherapy associated toxicities (time frame: 1 year)
Phase II, multicenter, open-label study	NCT02974803	Concurrent dabrafenib and trametinib with stereotactic radiation in patients with BRAF mutation-positive malignant melanoma and brain metastases	Arm A: 1–4 brain lesions treated with SRS concurrently with dabrafenib and trametinib Arm B: 5–10 brain lesions treated with SRS concurrently with dabrafenib and trametinib	Intracranial objective response (time frame: 2 years)

DLT dose limiting toxicities, *PFS* progression-free survival, *ORR* overall response rate, *fr* fractions, *SBRT* stereotactic body radiotherapy, *SRS* stereotactic radiosurgery (i.e., SBRT in 1 fraction)

events when they are associated with concurrent RT. Indeed, BRAF inhibitors lead to a cell-cycle end in G1 phase and thus increase radiosensitivity [37].

As far as immunotherapy in association with RT is concerned, the literature is also very limited. A case report described a generalized rash with concurrent RT and ipilimumab treatment [38]. In another case report, three patients with brain metastases were treated with ipilimumab and a single fraction of 20 Gy. One patient had a histologically proved radionecrosis and two other had a radionecrosis on MRI [39]. Brain hemorrhage was also reported for 6/15 patients (40%) treated with concurrent stereotactic radiosurgery and ipilimumab [40]. A literature review of all published trials combining radiation and immune checkpoint inhibitors in unresectable or metastatic melanoma patients had recently been published [41]. Only two small, prospective early phase clinical trials assessed the safety of ipilimumab with extracranial radiotherapy [42, 43]. With palliative dose RT, no abnormal toxicity was reported. Regarding intracranial RT, a dozen of retrospective studies have been conducted to address the safety of the combination ipilimumab/brain RT in patients with metastatic melanoma [41]. Radiation necrosis and intracranial hemorrhage were frequently reported, either with whole brain RT or with SBRT associated with ipilimumab. However, when study compared the association RT-ipilimumab to RT alone, toxicities were not different. Regarding nivolumab, no abnormal infield toxicity was reported in small cohorts of patients [44]. Ahmed et al. reported on 26 patients with 73 brain metastasis treated with nivolumab and SBRT within the 6 months of nivolumab administration [45]. Only one grade 2 headache was reported. No other neurologic or skin toxicities were observed. A study including a large series of patients who experienced nivolumab and RT was published: 46 patients had intracranial or extracranial palliative RT and nivolumab. They were assessed for acute toxicity only [46]. Nivolumab did not seem to change the toxicity profile of radiation, with only two grade 3 acute toxicities in the whole set of patients. However, further data are needed to explore the short-term and long-term safety of the immunotherapy–radiotherapy combination.

The type of drug administered with RT is certainly a major element to evaluate risks when mMM systemic drugs and RT have to be associated. However, irradiated volume, total dose and fractionation of RT should also probably be taken into account [25]. In our series, dose and fractionation were homogenous with moderate hypofractionation (i.e., median dose 30 Gy in ten fractions) and only 6.4% of SBRT. It did not allow us to assess a potential impact of dose or fractionation on toxicity. As to volume of RT, although not reported in our series, at least 75.5% of our patients had organs at risk in the field of RT (brain, vertebral, pelvis, rib, lymph nodes and abdominal mass volumes). All infield

grade ≥ 3 acute toxicities occurred during or following brain RT with vemurafenib. Our series suggests that extra-cranial palliative RT could be safely performed with mMM systemic drugs. Nevertheless, indications of brain RT should be carefully evaluated, especially with vemurafenib.

In short, concurrent administration of RT and systemic drugs of mMM seems to be safe, except BRAF inhibitors which have to be managed with extreme caution when associated with RT. Recommendations are available to guide management of mMM patients requiring RT [15, 16], although they are not supported by high quality data. Prospective data are required to extend what we know about the safety of such associations. Numerous prospective studies are ongoing associating anti-Braf and/or anti-CTLA4 or anti-PD1 or-PDL1 with concomitant RT in metastatic melanoma patients. These are listed in Table 6.

Compliance with ethical standards

Conflict of interest Authors declare having no conflict of interest.

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