Combination of immunotherapy and brain radiotherapy in metastatic melanoma: a retrospective analysis

Running title: Immunotherapy and brain radiotherapy in metastatic melanoma

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Summary

Background - Up to 40% of patients with metastatic melanoma (MM) develop brain metastases. Radiotherapy (RT) may potentiate the effects of immunotherapy (IO), even on distant sites (*abscopal* effect).

Material and Methods - We retrospectively analyzed all our MM patients treated with IO within 6 months before/after brain RT between 2012 and 2016. Progression free (PFS) and overall survival (OS) were estimated with Kaplan-Meier method and compared with controls treated with IO during the same period.

Results - Thirty-six cases and 25 controls were identified. Among cases, 23 patients received an anti-CTLA4, 13 an anti-PD1. Eighteen cases were treated with stereotactic RT (SBRT), 18 with whole-brain RT (WBRT). Median PFS from the beginning of RT was 4 months in first line and 2 months in second line. A third of the cases progressed at first evaluation after RT. Median OS from the beginning of RT was 7 months in first line and 4 months in second line. Median PFS and OS of each treatment line showed a trend towards inferiority as compared to those of controls.

Conclusion - Synergistim RT-IO was not observed in our case series. No cases of *abscopal* effect were seen and most patients underwent early systemic progression after RT.

Keywords: Brain; Immunotherapy; Melanoma; Metastasis; Radiotherapy.

Introduction

Brain metastases are common in metastatic melanoma (MM), as 10-40% of patients develop intracranial progression during their disease history. Complications of brain lesions (e.g. bleeding, stroke, epilepsy) are the direct cause of death in most of these cases. On the other hand, prognosis of melanoma patients with brain metastases is poor, with median survival ranging from 4 to 10 months in different studies [1, 2]. Significant therapeutic advances have been seen in the field of MM in recent years. The advent of *BRAF* inhibitors, immune checkpoint inhibitors (ICIs) and their combination/sequence has revolutionized clinical practice, leading to a significant survival prolongation in comparison with old cytotoxic strategies [3-5]. Recently, pre-clinical and limited clinical evidences have supported the existence of a synergistic effect between brain radiotherapy (RT) and IO in MM [6-8]. A potential rationale could lie in the radiation-induced damage to the blood-brain barrier, leading to a better drug penetration in the central nervous system (CNS). More plausibly, RT could unmask cancer antigens, increasing the activity of drug-stimulated immune cells on distant localizations [9, 10]. This hypothesis may explain the so-called *abscopal* effect, that is the evidence of disease response at non-irradiated sites during RT in patients with systemic malignancies. *Abscopal* effect can be observed in hematological tumors, but some cases have been described also in solid cancers including MM [11-13]. Given the contradictory evidences regarding this topic, we aimed to investigate the potential interaction between brain RT and IO in a single Institution cohort of patients with MM.

Methods

We identified a cohort of patients with MM treated with brain RT and IO outside clinical trials at our Institution between 2012 and 2016, and another cohort of controls treated with IO but not brain RT in the same setting and time frame. Data about clinical features, disease characteristics, previous treatments (surgery, systemic therapies and RT), disease response and outcome were retrospectively collected from Institutional database. Descriptive statistics were used to report clinical variables. Admitted IO included either anti-CTLA4 (ipilimumab 3 mg/kg i.v. d1 q21), or anti-PD1 (nivolumab 3 mg/kg i.v. d1 q14, pembrolizumab 2 mg/kg i.v. d1 q21). We considered as cases patients treated with external beam photon RT within 6 months since the beginning of IO, provided that no other oncologic therapies had been prescribed meanwhile. Stereotactic radiotherapy (SBRT) was administered as single fraction at a dose of 20-24 Gy. Whole-brain radiotherapy (WBRT) was administered as 10 fractions at a dose of 3 Gy each, up to a total of 30 Gy. Periodic evaluation of extra-cranial disease was performed with computed tomography (CT) and/or positron emission tomography (PET), at physician's discretion. CNS lesions were evaluated with magnetic resonance (MRI), or with CT scan in patients presenting contraindications to MRI. Radiologic evaluations were performed every 8-12 weeks, unless clinically indicated. Disease assessment was based on Response Evaluation Criteria for Solid Tumors (RECIST) v1.1 [14]. All patients signed an informed consent expressing agreement to the use of clinical data for research purposes at some time of their disease history. Progression-free and overall survival (PFS and OS, respectively) were estimated with Kaplan-Meier method. In particular, survival from RT, which was the primary objective of the analysis, was measured from the first day of RT to death or to data censoring. Comparisons between survival curves were performed with log-rank test. Chi squared or Fisher's exact tests were used to assess differences between categorical data, Mann-Whitney U test was applied for continuous variables. All analyses were two-sided and statistical significance threshold was set at 0.05. Statistical analyses were performed with SAS (version 9.4, SAS Institute, Cary, NC, USA).

Results

Patient and tumor characteristics

In the group of cases treated with both IO and brain RT, 36 patients were identified; 25 (69%) of them were men. Median age was 59 (range: 38-78). Seventeen patients were diagnosed with superficial spreading melanoma, 6 with nodular melanoma; histological classification was unknown in the remaining cases. Most patients (75%) had primary skin melanoma, 11% uveal melanoma, 3% mucosal melanoma. The majority of patients had distant visceral disease at the time of relapse (64%); the remaining ones had soft tissue metastases (skin in 14% of cases, lymph nodes with or without skin lesions in 22% of cases). Sites of distant disease were lung (n=10), bone (n=3), brain and other viscera (n=8 each). Baseline lactate dehydrogenase (LDH) serum level was higher than upper reference value in 4 cases (11%) at diagnosis of metastatic disease. *BRAF* gene was mutated in 9 patients, mostly *V600E* (8 cases); in the remaining 75% of patients, *BRAF* was wild type. Corresponding characteristics of the control group of patients are reported in Supplementary table 1.

Previous treatment characteristics

A total of 58% of patients received surgery at one or more metastatic sites, which consisted in skin/soft tissue lesions (10 cases), loco-regional lymph nodes (6 cases), lung nodules (3 cases), gallbladder lesions (2 cases) and brain metastases (2 cases). All patients received first line therapy, which consisted in IO in 22 cases (anti-CTLA4 in 18, antiPD1 in 4), *BRAF* inhibitor with/without *MEK* inhibitor in 6 patients, and chemotherapy in 7 patients. The most frequent reason for first line discontinuation was disease progression (53% of cases). Best response to first line therapy was complete response in 2 patients, partial response in 11 patients, stable disease in 6 patients, progressive disease in 13 patients; response was not evaluable in 4 cases. Median PFS of first line treatment was 4 months, median OS 7 months. Twenty-six patients were treated with second line therapy, consisting mostly in an anti-CTLA4 agent (50% of cases), followed by an anti-PD1 agent (35% of cases) and chemotherapy (15% of cases). Due to the high prevalence of ipilimumab administration in second line, most cases underwent regular conclusion of treatment (50%); in 19% of the remaining cases, treatment was interrupted for disease progression. No cases of complete response were seen in second line, but 4 patients obtained a partial response; the most frequently observed best response was progression (54% of cases). Median PFS and OS in second line were 2 and 4 months, respectively. Only 7 patients received a third line treatment for metastatic disease, consisting in an anti-PD1 agent in 4 cases, in an anti-CTLA4 one in 1 case, in cytotoxic chemotherapy in 2 cases. One patient obtained a brief disease stability,

whereas the remaining ones underwent rapid progression (2 patients) or died before the first radiologic evaluation (4 patients). Consequently, PFS and OS data were not evaluable in this setting. No significant differences in PFS could be observed stratifying patients for either treatment lines (p=.467), or specific ICI administered (p=.586). Similar results were observed for OS (p=.365 according to treatment line; p=.888 according to ICI received). Globally, the patients treated with brain RT and IO showed a tendency towards a worse outcome than controls treated with IO alone, without statistically significant differences in first line (p=.343 for PFS, p=0694 for OS) and a with worse PFS in second line (p=.027 for PFS, p=.933 for OS). Survival analyses according to treatment variables are detailed in Table 1 for the group of cases, in Supplementary table 1 for the group of controls.

Brain progression and specific treatments

Among cases, median interval from diagnosis to brain progression was 25 months (range: 5-180 months). Most patients presented multifocal brain disease (75% of cases) and all had concomitant extra-cranial localizations at the time of brain progression (skin and soft tissues in 25 cases, lung in 18 cases, bone in 3 cases, other viscera in 17 cases). Brain disease was symptomatic in almost half of the patients (47%); 10 of them required an anti-epileptic therapy, 27 of them required steroids. Symptomatic patients had a significantly shorter PFS than asymptomatic ones (p=.049), without differences in OS (p=.266). The administration of steroids and anti-epileptics did not determine differences in PFS (p=.345 and .386, respectively) or OS (p=.815 and .254, respectively). All patients were treated with RT, either SBRT (50%) or WBRT (50%). RT was administered within 6 months since the beginning of ipilimumab in 23 patients, within 6 months since the beginning of nivolumab/pembrolizumab in the remaining 13 patients. Median time between the diagnosis of CNS metastases and the beginning of RT was 5 weeks (range: 1-10 weeks). In patients receiving SBRT, median radiation dose was 24 Gy (range: 18-25 Gy) in single fraction. Out of the 18 patients receiving WBRT, 6 (33%) did not complete the treatment plan due to intracranial complications. Thus, only 12 subjects received a total of 30 Gy in 10 fractions. Intra-cranial disease response was not evaluable in 20 patients, due to rapid clinical deterioration or death before the first radiologic evaluation. Among the remaining cases, brain response was mostly progression (11 cases), with a small number of stabilizations (3 cases) and partial responses (2 cases). Median time from RT to intra-cranial progression was 14 weeks (range: 5-56 weeks). Only a few patients could receive subsequent brain local therapies, consisting in either further RT (3 cases), or surgery (2 cases, as a consequence of acute complications). Four cases of neurologic toxicity potentially related to RT (including bleeding and epilepsy) were reported. No apparent exacerbation of IO toxicity due to RT was observed, as no cases of grade ≥3 adverse events occurred during concomitant/sequential administrations of such treatments.

Fourteen patients (39%) presented extra-cranial progression after brain RT, with a median time to progression of 8 weeks. The most common sites were lymph nodes and lungs (9 patients each), followed by other viscera (6 patients), skin (5 patients) and bone (3 patients). No differences in PFS were observed among patients with intra- and extra-cranial progression after RT (p=.121). After a median follow-up of 2 months (range: 0-18 months) from RT, 9 patients were alive and under treatment, 20 were dead, 7 were lost at follow-up. Median OS from RT was 6 months, without difference among cases treated with SBRT and WBRT (median OS 7 and 5 months, respectively; p=.1455).

Discussion

During the last years, significant efforts have been spent to ameliorate prognosis of patients with MM and encephalic disease [15]. RT is almost always needed to palliate neurologic symptoms and to obtain intra-cranial disease control, due to the scarce penetration of ICIs across the blood-brain barrier [16]. RT has a strong cytotoxic effect, mediated by the generation of oxygen free radicals capable to damage cancer DNA and proteins. It is likely that cell lysis leads to release of cancer antigens, increasing their presentation to immune cells and activating a specific anti-tumor response. On such a speculative basis, it was hypothesized that RT and IO could have a synergistic effect, with an increase of drug efficacy as a consequence of local RT [17, 18]. A consistent amount of pre-clinical data supports the hypothesis of an *abscopal* effect due to concomitant administration of IO and RT [7,8]. Nonetheless, clinical experiences provided more contradictory data, with some retrospective case series documenting a synergism between RT and IO, and others showing absence of benefit from combined treatments [19]. For example, Silk et al. reported a significant OS prolongation in patients with MM treated with SBRT and ipilimumab, in comparison with control cases receiving RT alone (19.9 *versus* 4.0 months, p=.009). Apparently no effects were seen with WBRT in the same setting [8]. On the other hand, Patel et al. failed to document any differences in PFS and OS in a similar case series of melanoma

patients treated with ipilimumab and brain RT, though in absence of toxicity concerns [9]. Recent data about anti-PD1 agents in concomitance with RT are more encouraging [20-22]. For example, Choong et al. reported a promising OS of 20.4 months with SBRT administered within 6 weeks from an anti-PD1. The result was more unsatisfactory with anti-CTLA4 (median OS 7.5 months). Gaudy-Marqueste et al. evaluated a cohort of patients with metastatic melanoma treated with targeted drugs, anti-PD1 agents or chemotherapy in concomitance with SBRT, finding a particularly strong synergy with the combination of anti-PD1 and RT (median OS 14.8 months). As prospective data are lacking, the issue of identifying any synergy between RT and systemic treatments for MM remains unsolved. In this retrospective analysis, we could not find evidences of benefit for combined brain RT and IO. Indeed, no differences in outcome were observed in either the global population, or specific subgroups stratified for treatment line, ICI administered, RT technique, and intra/extra-cranial disease extent. The only significant observation concerned the presence of neurologic symptoms at brain relapse, which were related to a shorter PFS without differences in OS. Globally, patients outcome was poor, with most cases undergoing progression at first evaluation after RT, and a particularly short OS of only 6 months from brain local treatments. Notably, also extra-cranial disease showed a tendency towards rapid progression and no cases of *abscopal* effects were seen. Neither immune-mediated toxicity nor neurologic adverse events seemed to be worsened by the concomitance of the two approaches. The scant outcome of these patients was confirmed by the comparison with a control group treated with IO but not brain RT, showing a tendency towards worse PFS and OS for the patients receiving the combination of IO and RT. It has to be underlined that the control patients differed from the cases in the lower prevalence of brain disease and this point itself can explain their better prognosis. Nonetheless, such a comparison underlines the conclusion that in our case series the concomitant effect of IO and RT does not overcome the negative prognostic impact of brain disease itself. Different hypotheses can be proposed to explained the negative result of the analysis. First of all, the frequent administration of steroids to patients with intracranial disease, forced by the high prevalence of neurologic symptoms, might have weakened their immune response thus hiding a potential synergistic effect of IO. Notably, no evidence of synergy could be observed even in patients not receiving steroids, although the small number of these cases limits the possibility to draw inferences about this point. Secondarily, two thirds of the patients presented multifocal brain disease. In comparison with the situation of a solitary encephalic nodule or a small number of brain metastases, such a disease extension is generally associated to a poor prognosis and a limited benefit from RT. The similar outcome of patients with intra- and extra-cranial progression suggests an adjunctive consideration. It may be argued that encephalic progression entails a worse prognosis than systemic one. The absence of this difference in our case series may suggest that our patients presented a large burden of systemic disease in adjunct to brain metastases. Indeed, the vast majority of them had visceral metastases (lung, liver, or both), and only a minority developed brain progression in presence of soft tissue disease alone. The concomitance of brain lesions and a high burden of extra-cranial disease suggests that our population may have a particularly unfavorable prognosis, so that even the best combination of treatments might not induce a benefit. Another key point that could help to interpret the results is the fact that half of our patients (18 subjects) received SBRT. Some preclinical models have shown that *abscopal* effect is usually not observed after single fraction of RT, but only with fractionation [25]. This could be explained by the fact that a repeated radiation-induced cell damage could lead to a more effective tumor antigen presentation to immune cells. The limited number of our patients that completed the WBRT (12 cases) might help to interpret the negativity of our results. At the end, the long time interval between RT and IO (6 months) was chosen in order to include a higher number of patients in the analysis and was in line with previous works [9]. Although the prolonged effect of IO on immune response and the possibility to obtain disease control also after the conclusion of treatment support this rationale, such a wide time range between systemic and local therapy may have interfered with the results. However, it has to be underlined that most of the patients (70%) received RT within 3 months from the beginning of IO and 33% of them received RT within the 4 weeks before the beginning of IO. Therefore, a radical change of the results excluding the cases with the longest time span is unlikely. The present study has some limitations that have to be evidenced. It reports the results of a small single Institution experience, with a limited number of cases. The retrospective collection of cases and controls led to unavoidable imbalance in the proportion of patients with brain disease, with potentially confounding effects on prognosis. Medical treatment was not homogeneous, as some patients received chemotherapy, some other IO with either ipilimumab or nivolumab or pembrolizumab. ICIs were

administered in different treatment lines, with likely confounding effects on OS. RT was started at quite different times from IO (in concomitance, before or after treatment, with various length of drug interruption during local radiation therapy). At the end, the wide time span of the cases enrolled (from 2012 to 2016) led to lack of homogeneity between available treatments, which are not completely in line with current practice (e.g. high prevalence of ipilimumab and WBRT over anti-PD1 agents and SBRT, respectively). This could be of particular concern in consideration of the most recent data showing favorable outcome with the combination of anti-PD1 and SBRT, but quite worse results with anti-CTLA4 [22-24]. With all these limitations, the present study seems to evidence absence of synergy between brain RT and ICIs in MM. Given the limited and contrasting data present in literature, this issue remains open and prospective data are needed to gain definitive evidence about it. Indeed, the increasing treatment options for MM, including newer strategies of IO (e.g. combinations of anti-CTLA4 and anti-PD1, novel drugs as anti-LAG3 and anti-TIM3, etc.), require urgent clarification of interactions with RT, whose effect may be crucial to impact on the outcome of patients with brain disease.

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