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Radiotherapy and immunotherapy: Can this combination change the prognosis of patients with melanoma brain metastases?

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ABSTRACT

Brain metastases are a common occurrence in patients with melanoma. Prognosis is poor. Radiotherapy is the main local treatment for brain metastases. Recently, immunotherapy (i.e. immune checkpoints inhibitors) showed a significant impact on the prognosis of patients with metastatic melanoma, also in the setting of patients with brain metastases. Despite various possible treatments, survival of patients with melanoma brain metastases is still unsatisfactory; new treatment modalities or combination of therapies need to be explored. Being immunotherapy and radiotherapy alone both efficient in the treatment of melanoma brain metastases, the combination of these two therapies seems logical. Moreover radiotherapy can improve the efficacy of immunotherapy and the immune system plays a relevant role in the action of radiotherapy. Preclinical data support this combination. Clinical data are more contradictory. In this review, we will discuss available therapies for melanoma brain metastases, focusing on the preclinical and clinical available data supporting the possible synergism between radiotherapy and immunotherapy.

Introduction

Unfortunately, brain metastases are a common finding in patients affected by solid tumours, occurring in 10–30% percent of adults with cancer [1]. Melanoma is the third cause of brain metastases after lung and breast cancers [2]. It is estimated that approximately 10–40% of all patients with advanced stage melanoma will receive a diagnosis of brain metastases during the course of their disease [3]. If we consider data coming from autopsy studies, numbers are even more impressive, since up to 75% of patients with malignant melanoma are found to have brain metastases [4]. Moreover, intracranial disease progression is directly the cause of death in 20–54% of patients with metastatic melanoma [5]. Prognosis of patients with melanoma brain metastases (MBM) is poor, with a median survival of 4–5 months [6,7]; even in selected patients, treated with aggressive local approaches, like surgery or radiosurgery, the median overall survival (OS) ranges around 8 to 10 months [8].

The reason of this very high inclination of melanoma to develop brain metastases is not yet understood. Published experiences focused on predictive factors for the development of MBM showed conflicting results [2,7].

Patients with metastatic melanoma are living longer, due to the increased availability of efficient systemic therapies. Considering brain metastases as an almost inevitable part of the disease progression, if patients survive long enough, an increased number of melanoma patients with brain metastases is expected in the next years. Therefore, more valid and efficient therapeutic approaches for intracranial disease are urgently needed. We conducted this review of the available literature, exploring the possibility of a synergistic combination between stereotactic radiosurgery (SRS) and immunotherapy.

Treatment modalities

Historically, local therapies, i.e. surgery or radiotherapy (whole brain radiotherapy or SRS), have been the mainstay of treatment, but with limited success. Furthermore, most of the studies assessing the efficacy of these treatments in brain metastases have recruited patients with disease originating from various primary sites, with only a small proportion of patients affected by melanoma. The combination of local approaches with traditional systemic therapies did not add significant benefits.

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Choice of the best treatment for each individual patient is a difficult challenge, depending mainly on the number, size, and site of lesions; the status of extracranial metastases; the performance status and the prognosis of the patient [9].

Local approaches

Surgery

Traditionally surgical removal of MBM is considered as a mainstay treatment.

Surgery can result in rapid improvement of neurological symptoms, especially in case of large brain metastases. In some cases, surgical removal is also indicated for histological confirmation, for example in cases of unknown primaries. In patients with one or two brain metastases, good PS and minimal or absent systemic disease, surgery can improve quality of life and even survival [10,11].

However, this subset of patients is really limited. More often, surgical removal is not feasible because of number or sites of lesions, PS, widespread dissemination of the disease. The largest study on surgery for MBM is a retrospective series on 686 patients, in which OS in patients treated with surgery (8·7 months) or surgery plus radiotherapy (8·9 months) was significantly longer than for patients treated with radiotherapy alone (3·4 months) or supportive care (2·1 months; $p < 0.001$) [12]. However, resection alone is correlated with high local failure rates (59% at 2 years) [13].

Radiotherapy

Radiotherapy, historically in the form of whole brain radiotherapy (WBRT) and more recently as SRS, is currently the gold standard treatment in patients with non-resectable MBM. Conventionally, SRS is prescribed in patients with few brain metastases and with a good PS, while WBRT is considered in case of multiple brain metastases and/or poor performance status or bad prognosis. Considering the relative radioresistance of melanoma cells when treated with small radiation doses, SRS delivering higher doses in single or few fractions seems the ideal treatment for MBM [14].

WBRT. Historically, WBRT has become a de facto (but not evidence-based) standard treatment for MBM. WBRT can improve intracranial disease and delay neurological decline if compared with best supportive care, however median OS after WBRT remains unsatisfactory at 2–5 months [15]. Young patients with a good PS and no extracranial disease have the best prognosis after WBRT [16].

The most commonly prescribed schedule is 30 Gy in 10 fractions, since none of the other fractionations studied demonstrated superiority in terms of survival, neurological function or symptoms control [17].

Apart from the dismal prognosis, WBRT is also loaded with a detrimental effect on quality of life and neurocognitive functions, as shown by Chang et al. in a randomized trial few years ago [18]. The risk of neurocognitive decline may be as high as 49% after WBRT [19]. Similar results were also obtained in the NCCTG N0574 phase III trial. A decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Moreover, adjuvant WBRT did not improve OS despite better brain control [20].

WBRT can be also used as an adjuvant treatment after surgery or SRS. Control of intracranial disease is improved with the combined modality, but there is no OS benefit resulting from randomized trials [13,21].

SRS. Stereotactic radiosurgery is a RT technique that allows the delivery of very high doses to the lesion with an excellent sparing of surrounding normal tissues. Usually prescribed as a single dose, SRS can be delivered with Gamma Knife or with linear accelerators. With this technique, the efficacy of the treatment is similar to surgical removal of the metastases, with local control rates in the range of 80–85% [8]. There are no comparative studies between surgery and SRS. However, SRS can be the treatment of choice also for small lesions, for lesions in the eloquent area or for lesions inaccessible to surgery. With SRS more lesions can be treated in the same session, usually up to four metastases, however there are some data supporting the use of SRS in patients with ten or more lesions [22]. Moreover, thanks to the high precision of SRS, the risk of neurocognitive sequelae is reduced, with a reported incidence of late neurological toxicity of 4% [18], significantly lower than WBRT. Median survival in patients with MBM treated with SRS is 5–11 months [23].

Surgery/Radiosurgery +/− WBRT. Combined modality treatment is associated with a reduced risk of death: median OS after WBRT alone was 2.9 months, compared to 11.1 months and 13.1 months in patients undergoing surgery plus WBRT or SRS plus WBRT, respectively [9].

Moving from these results, it has been discussed if WBRT was really necessary for all patients undergoing a definitive local treatment for brain metastases, surgery or SRS. Large randomized trials were designed, to address this issue.

Results were consistent, showing that local control after local treatment is not improved by WBRT, but the addition of WBRT reduces the risk of new brain metastases [19,24,25]. However, none of these studies showed a significant advantage in terms of OS. For instance, the EORTC 22952-26001 study [13] randomized 359 patients undergoing surgery ($n = 160$) or SRS ($n = 199$) and were randomized to no further treatment or WBRT (30 Gy in ten fractions). WBRT improved 2-year relapse rates and reduced the incidence of new brain metastases, however no improvement in OS was reported.

The lack of survival benefit is probably related to the efficacy of delayed salvage therapy in case of new brain metastases, such as new SRS or delayed WBRT [26].

Therefore, considering the non detrimental impact on OS and the benefits in terms of quality of life and neurocognitive functions, avoidance or delay of WBRT in patients with 1–4 brain metastases treated with surgery or SRS is usually recommended.

Systemic therapies

Until recently, the therapeutic efficacy of systemic therapies for MBM was unsatisfactory. Conventional systemic cytotoxic therapies such as dacarbazine, temozolomide, or fotemustine all showed limited activity against MBM [27,28]. The main limitation for the efficacy of systemic therapies is the presence of the blood–brain barrier, which prevents the access of many systemic drugs to brain metastases [29], especially agents consisting of large and hydrophilic molecules.

Traditionally, brain was considered an immunologically privileged site because of the restriction of the conventional circulation of lymphocytes and antibodies by the blood–brain barrier and also because of immunosuppressive elements that limit T-cell activation [30,31]. These regulatory processes may complicate and hinder the treatment of cerebral melanoma metastases using immune-based therapies. Indeed, high-dose interleukin 2 has proved disappointing for treatment of brain metastases, with a response rate of 6% in a retrospective review [32].

Luckily the scenario changed recently.

Indeed, it has been demonstrated that activated T cells can patrol the central nervous system (CNS), crossing the blood–brain barrier [33,34]. These observations stimulated the strategy of T-cell