On demand Gamma-Knife strategy can be safely combined with BRAF inhibitors for the treatment of melanoma brain metastases

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Background: Both Gamma-Knife radiosurgery (GKRS) and BRAF inhibitors (BRAF-I) have been shown to be useful in melanoma patients with brain metastases (BM)s, thus suggesting that it could be interesting to combine their respective advantages. However, cases of radiosensitization following conventional radiation therapy in BRAF-I treated patients have raised serious concerns about the real feasibility and risk/benefit ratio of this combination.

Patients and methods: Review by two independent observers of brain magnetic resonance imaging (MRI) follow-up pictures, and volume and edema quantifications, and survival assessment in all patients who had been treated by GKRS and BRAF-I at a single institution.

Results: Among 53 GKRS carried out in 30 patients who ever received BRAF-I and GKRS, 33 GKRS were carried out in 24 patients while under BRAF-I treatment, from which only 4 with an interruption of BRAF-I. The 20 other GKRS were carried out in 15 patients (including 9 of the 24) before initiation of BRAF-I treatment. No case of radiation-induced necrosis and no scalp radiation dermatitis occurred. A >20% increase in volume was observed in 35 of the 263 BM treated by GKRS (13.3%), but only 3 clear-cut edemas and 3 hemorrhages were detected within 2 months after GKRS, and 4 edemas and 7 hemorrhages later. Neither the MRI features nor the incidence of the volume changes, hemorrhage and edema were deemed unexpected for melanoma BM treated by GKRS. Median survival from first GKRS under BRAF-I and first dose of BRAF-I were 24.8 and 48.8 weeks, respectively.

Conclusion: This series does not show immediate radiotoxicity nor radiation recall, in melanoma patients with BRAF-I whose BMs are treated by GKRS. Interrupting BRAF-I for stereotactic radiosurgery (SRS) of BM seems useless, although it is still advised for other radiation therapies. The potential benefit of combining SRS and BRAF-I can be safely tested.

Key words: BRAF inhibitors, Gamma-Knife radiosurgery, radiosensitzation, brain metastasis, metastatic melanoma

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Introduction

Brain metastases (BMs) often develop during metastatic melanoma (MM) course and considered responsible of death in half of patients [1]. Stereotactic radiosurgery (SRS) including Gamma knife (GKRS), Linac radiosurgery, and Cyberknife is considered an effective strategy in the treatment of BM in metastatic MM either as an alternative to surgery for solitary BM with the advantage of excellent local control rates with minimal invasiveness, or as an effective palliative strategy for multiple BM because several lesions can be treated at the same time, and sessions can be repeated ‘on demand’ as often as required [2, 3].

BRAF inhibitors (BRAF-I) have demonstrated a high response rate and survival benefit in BRAF-V600-mutated MM patients [4, 5]. As patients with BM were often excluded from clinical trials, data regarding BRAF-I efficacy in the treatment of BM are limited but encouraging [6, 7]. In a phase II study with dabrafenib, the intracranial response rates were 39.2% in 74 non-pretreated V600E-mutant patients and 30.8% in 65 previously treated V600E-mutant patients [6] and preliminary results with vemurafenib seem within the same range [7].

The combination of a BRAF-I and SRS is thus potentially useful in the management of MM patients with BM. It can be used as a rescue strategy in patients treated by BRAF-I, in case of a heterogeneous progression in the brain despite an overall disease control, and can be repeated if needed. Alternatively, in patients who develop multiple metastases including brain, SRS can be used for immediate control of threatening BM, while BRAF-I are started at the same time to treat metastases in other organs, and also possibly to control undetectable BM.

These combination strategies are obviously worth being tested in prospective trials. However, acute radiotoxicity and radiation recall phenomenon have been recently reported, thus questioning about the actual feasibility of combining the two strategies [8–10]. Although most of the reported cases of radiosensitization corresponded to skin toxicity easily manageable, a few severe visceral complications, some of them fatal, have also been reported [11], leading the medical community to recommend at least a withholding of the BRAF-I before any radiation therapy.

Nevertheless, data regarding the cerebral potential radiosensitizing effect of BRAF-I remain quite limited with the largest series of combination of radiotherapy and BRAF-I treatment reporting only 12 cases treated by variable types of radiotherapy [12]. Furthermore, radiosensitization issues with BRAF-I is likely to be overestimated [13] by a publication bias.

Whether or not this very attractive strategy of combination of on-demand SRS and BRAF-I is safe is of crucial importance for patients with MM–BM and is actually a matter of active discussion.

Our objective was to assess the safety of this combination by a retrospective review of a series of 30 patients treated by both BRAF-I and GKRS.

Methods

Population

Patients treated by BRAF-I in our department (University Hospital La Timone, Marseille, France) for a stage IV MM, and who underwent at least one GKRS between August 2010 and June 2013 were included in this retrospective study.

Gamma-Knife procedure

All patients were treated with the GKRS Perfexion (Elekta, Stockholm, Sweden) in the same unit (University Hospital La Timone). Imaging-compatible Leksell stereotactic frame (Elekta Instrument) was applied to the patient’s head under local anesthesia and mild sedation. Neuroimaging consisted for all patients of a stereotactic 3D T1-weighted postcontrast sequences (double dose of gadolinium) (magnetization PREPARED RAGE Gradient ECHO or MP-RAGE, Siemens), a stereotactic magnetization transfer (MT) sequences and a stereotactic Brain CT scan. Selection of dosimetric parameters (dose, marginal isodose, number of isocenters) was made according to size, shape, location, and relationship of the BM to critical structures based on prior experiences in our and others centers, and on the prediction of complications determined by ‘integrated logistic formula’ [14]. Total dose was delivered in a single session. The marginal prescription dose ranged between 20 and 28 Gy at the 50% isodose in the vast majority of cases (maximum dose 40–56 Gy). Particular attention was paid to conformality and selectivity of the dose planning.

Neuroimaging

In all patients, cerebral imaging consisted of injected CT scan or magnetic resonance imaging (MRI) scans (MP-RAGE, 3D T1-weighted postcontrast (1.5 × 1.5 × 1.5) Flair and T2-weighted to assess edema) carried out immediately before GKRS (same day), at 2 months, and every 3 months thereafter according to the usual policy of follow-up in our GKRS department. Neuroimaging assessment was carried out on MRI scans for 22 patients (78.5%), on both MRI and injected CT scan in 2 and only in injected CT scan for 4 patients.

Outcome measures for radiotoxicity

All patients who underwent GKRS during BRAF-I were assessed for radiotoxicity. Patients who had at least one GKRS before BRAF-I were assessed for radiation recall.

Clinical data. The medical records were reviewed to assess other potential complications including neurological symptoms and lesions of the scalp.

Radiological detection of unexpected radiotoxicity by experts.

Each of the follow-up cerebral imaging was analyzed by two neurosurgeons (RC and CD), highly experienced in GKRS who were asked to report any neuroimaging alterations in the follow-up they would deem unusual in relation to the natural history of a BM treated by GKRS or that they would consider an adverse radiation effect. Both were blind to when the patient has received BRAF-I, and whether it was interrupted or not.

Objective measures of brain metastases after GKRS.

It is well established that changes in volume of contrast-enhanced area, edema, and hemorrhage are usually seen in the natural history of BM treated by GKRS, and thus no standardized radiological measure can permit to easily define success or failure of GKRS, nor to differentiate early recurrence from an adverse radiation effects [15]. A semiquantitative scale from + to +++ was used to quantify edema. In order to assess potential radiotoxicity, we report the proportion of BM treated by GKRS with a >20% volume increase in BM, and describe edema.

Volume assessment of each treated lesion was done with Leksell Gamma Plan 10.1.1 software (Elekta, Stockholm, Sweden) allowing to contour the lesion before and at each step of the follow-up. The contouring was carried out both manually and with semiautomatic segmentation tool.


efficacy indicators. This study cannot provide any efficacy data, but as indicators, we calculated overall survival (OS) (i) from the date of first GKRS under BRAF-I to the date of death and (ii) from the first dose of BRAF-I to the date of death. The ‘time to new brain metastasis’ was also calculated from the date of first GKRS carried out under BRAF-I to the date of the first occurrence of a new BM.

statistical analysis

Statistical analysis was carried out using PASW Statistics version 17.02 (IBM SPSS, Inc., Chicago, IL). Probability of survival was estimated using the Kaplan–Meier method.

results

population and treatments

population. Overall, 30 patients case were included. Characteristics are given in Table 1. GKRS was carried out under BRAF-I treatment in 24 of the 30 patients, without any BRAF-I interruption in 20 of the 24. BRAF-I was transiently interrupted in 4 of the 24 patients when publications were highlighting a real risk of radiotoxicity (>2.5 half-lives of Vemurafenib or Dabrafenib, before and after GKRS). Of the 24 patients, 9 also had at least one GKRS before initiation of BRAF-I treatment. An additional 6 patients outside the 24 had GKRS exclusively before BRAF-I. Median follow-up was 21 weeks (8–82.5) after first GKRS carried out under BRAF in the 24 patients, and 35 weeks (8–82.4) after BRAF introduction in the 30 patients.

BRAF-I. Most of the patients (26/30, 86.6%) received vemurafenib, the others dabrafenib. Five patients of the 30 received the BRAF-I in the setting of a clinical trial, 18 in the setting of a temporary access program, and 7 after marketing approval of the drug. Twenty from the 30 patients received a full daily dose of the BRAF-I, whereas the dose was decreased either transiently or definitively in the other 10.

GKRS treatments. Of the 30 patients with combined BRAF-I and GKRS, 20 had only one GKRS session and 10 underwent repeated GKRS. Overall, 53 GKRS sessions were carried out (Table 2) to treat 263 BM in the 30 patients, 20 GKRS before initiation of BRAF-I treatment, and 33 GKRS under BRAF-I treatment. Of these 33 GKRS sessions, 17 sessions were carried out in the first day of BRAF-I treatment aiming at an immediate control of BM, and 16 sessions later because of a cerebral progressionunder BRAF-I. Of the 53 GKRS treatments, 13 (24.5%) were targeting a unique BM, and 40 (75.47%) multiple BM. One patient has previously undergone cerebral radiotherapy for a glioblastoma (+adjuvant temozolomide).

outcomes

clinical events. No scalp radiation dermatitis occurred during the follow-up. Six patients (20% of the 30 patients) presented neurological symptoms during follow-up including confusion (n = 1), paresthesia (n = 1), and hemiplegia (n = 1) within 2 months post GKRS, and intracranial hypertension (n = 1), convulsion on meningitis (n = 1), and aphasia (n = 1) after 4 months post the last GKRS. All these patients suffered from highly metastatic cerebral diseases with 4–20 BM by patient. Five patients were under antiepileptic medication before GKRS and 5 under corticosteroids. One of the patients was shortly hospitalized (3 days) due to intracranial hypertension requiring IV corticosteroids. We do not have to increase the steroids dose of the others.

radiological detection of unexpected radiotoxicity by experts. None of images were deemed unusual or unexpected in the usual natural history of a BM treated by GKRS by the two experts.

objective volumetric measures, edema, and hemorrhage. It was carried out in 28 patients, since 2 patients died of highly disseminated disease without any neurological symptom before the first brain imaging at 2 months. An >20% increase in treated BM volume was observed in 35 of the 263 BM treated by GKRS.

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<th>Table 1. Patient characteristics</th>
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<td>Sex</td>
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<td>Mean age (years)</td>
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<td>BRAF-I</td>
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<td>AJCC (at BRAF-I introduction)</td>
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<td>Number of GKRS (number of patients)</td>
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*9/20 also underwent GKRS before BRAF-I.

b>2 half-lives of the BRAF-I.

GKRS, Gamma-knife radiosurgery; BRAF-I, BRAF inhibitor.
(13.3%), including 26 of the 201 BM treated while under BRAF-I (12.93%), 2 of the 8 BM treated after transient interruption of the BRAF-I (25%), and 7 of the 54 BM who had GKRS before the introduction of the BRAF-I (12.96%), this last group being assessed only for a potential radiation recall.

When focusing on the immediate toxicity (at the 2-month brain imaging) of concomitant administration toxicity (22 of the 28 patients), 11 BM had a >20% volume increase, including 9 displaying some degree of edema (+ to ++), from which 2 severe edema (+++) and 2 hemorrhages (0.99% of the treated BM) in the 18 patients who underwent GKRS without BRAF-I interruption, and 1 severe (+++) edema and 1 hemorrhage (12.5% of the treated BM) in the 4 patients who interrupted BRAF-I at time of GKRS. When focusing on late radiotoxicity, 28 patients were assessable, including 22 with concomitant GKRS and BRAF-I, and 6 with GKRS exclusively before BRAF-I (thus only assessable for recall). Four severe edemas (+++) and seven hemorrhages (1.52% and 2.66% of the treated BMs, respectively) were detected later during the follow-up imaging (>4 months post GKRS).

**efficacy outcomes.** At the time of the analysis (18 October/2013), median time to new BM from first GKRS under BRAF-I was 12.85 weeks [95% confidence interval (CI) 11.6–14.07] (Figure 1A). Median OS from first GKRS under BRAF-I was 24.8 weeks (95% CI 10.1–39.6) (Figure 1B). Median OS from first dose of BRAF-I was 48.85 weeks (95% CI 30.62–67.08) (Figure 1C) and 6-month survival estimate was 78.8%.

**discussion**

Our series of 30 patients who have been treated with GKRS and BRAF-I at any time of their disease, 20 of them receiving concomitant treatment, does not provide evidence for any increased radiation toxicity in patients with BRAF-I treatment.

No scalp radiation dermatitis was observed. No images were considered as resulting from immediate radiosensitivity or radiation recall by the two observers who reviewed the follow-up neuroimaging. This assessment of images by GKRS experts, who see hundreds of cases every year, is probably the best way to detect an abnormal radiotoxicity. Indeed, objective measures are difficult to interpret. A >20% increase in volume after GKRS was noticed in 35 lesions (13.3%) including 19 (7.22%) for which no edema at all, nor hemorrhage were noticed. However, it is impossible to attribute this volume change to an abnormal radiotoxicity, since it corresponds in most cases to the natural evolution after RS [15] or even to a local recurrence. Moreover, it is unlikely that volume increase was linked to a BRAF-I-induced radiotoxicity, since the proportion of BM with >20% volume increase after GKRS was higher in patients who interrupted BRAF-I for GKRS, than in patients who did not interrupt BRAF-I. The low bleeding rate in this series (<2.66%) given the natural propensity of BM of MM for bleeding [16, 17] does not support any increased risk resulting from the combination of GKRS and BRAF-I. Similarly, the <1% rate of edema seems rather in the lower range of usually observed events in BM treated by GKRS [2]. Furthermore, hemorrhage and edema were also present in the cases, in which BRAF-I was interrupted before GKRS. Although we cannot exclude any radiotoxicity in the two patients, who died before the first control of brain MRI at 2 months, none had neurological or skin symptoms, and death can be easily explained by the peculiar severity of the disseminated metastatic disease.

Previously published series of brain radiotherapy together with BRAF-I [12, 13] are small, heterogeneous in terms of radiotherapy procedures summing up very different procedures including whole brain radiotherapy (WBRT), partial brain radiotherapy (PBRT), and SRS, and do not permit to draw any conclusions. In Narayana series [12], vemurafenib was administered before radiation therapy (n = 7) or during radiation therapy (n = 5) in 12 patients treated either with WBRT (n = 3), SRS alone (n = 6), PBRT (n = 3) or SRS combined to PBRT (n = 1). Only one case of suspected radiation necrosis occurred 3 months after vemurafenib introduction in a patient previously

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**Table 2.** GKRS treatments

<table>
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<tr>
<th>Timing of GKRS as to BRAF-I treatment</th>
<th>53 GKRS sessions in 30 patients treating 263 BM</th>
<th>33 GKRS sessions under BRAF-I treating 209 BM</th>
<th>20 GKRS sessions before BRAF-I treating 54 BM</th>
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<tr>
<td>GKRS together with BRAF-I introduction</td>
<td>29 GKRS sessions with no interruption of the BRAF-I treating 201 BM</td>
<td>4 GKRS sessions with transient interruption of the BRAF-I* treating 8 BM</td>
<td>20 GKRS sessions before BRAF-I</td>
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<tr>
<td>BRAF-I introduction</td>
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<td>GKRS after cerebral progression under BRAF-I</td>
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<tr>
<td>BRAF-I introduction</td>
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<tr>
<td>GKRS before BRAF-I introduction</td>
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<tr>
<td>Indication of GKRS</td>
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<tr>
<td>Unique BM</td>
<td>17 GKRS sessions</td>
<td>0 GKRS</td>
<td>NR</td>
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<tr>
<td>Multiple BM</td>
<td>12 GKRS sessions</td>
<td>4 GKRS sessions</td>
<td>NR</td>
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<td></td>
<td>NR</td>
<td>NR</td>
<td>20 GKRS sessions</td>
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<tr>
<td></td>
<td>5 GKRS (5 BM treated)</td>
<td>1 GKRS (1 BM treated)</td>
<td>7 GKRS (7 BM treated)</td>
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<td>24 GKRS (196 BM treated)</td>
<td>3 GKRS (7 BM treated)</td>
<td>13 GKRS (47 BM treated)</td>
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*a>2 half-lives of the BRAF-I.
BM, brain metastasis; GKRS, Gamma-knife radiosurgery; BRAF-I, BRAF inhibitor.
treated with two SRS procedures and a PBRT. The diagnosis of radiation necrosis was however not certain with PET/CT documented hypermetabolism of the lesion, and the accumulation of the three radiation therapies in the same field could explain by itself such an adverse event, out of the context of BRAF-I treatment. In a recently reported small series of five patients who underwent three WBRT and two SRS under BRAF-I, there was no evidence of increased radiotoxicity although an easily manageable radiation dermatitis (grade 2 and 1) only occurred in patients treated with WBRT [13].

The absence of radiosensitization or radiation recall in our series does not exclude possible complications with a combination of GKRS and BRAF-I, but at least suggests that it is very unusual. Clearly, there is a bias for reporting complications rather than the no-problem situations, which may lead to overestimate the risk. It must be kept in mind that in terms of radiobiology, SRS is extremely different from the classical radiation therapy modalities. Most of the energy is delivered to the target while sparing the surrounding healthy tissue whose residual radiation proves negligible or insignificant below that of a single session of radiation therapy (2–3 Gy). The tumor volume is the main limiting factor in SRS since the volume of the irradiated healthy brain increases when larger metastases are treated. This can result in formation of a local edema around the irradiated target typically 6–9 months after SRS. Adverse radiation effects are seen in larger metastasis and are uncommon in BM smaller than 2.5 cm [2]. Therefore, it may not be be relevant to extrapolate any radiotoxicity concern from classical radiation therapy to SRS, even in association with BRAF-I. Interrupting BRAF-I treatment of SRS may not be relevant. Metastases control by BRAF-I may be jeopardized in case of drug interruption in these high-risk metastatic patients, although no data really assessed how much discontinuation of BRAF-I can be detrimental to patient prognosis. Furthermore, possible radiosensitization, if any, by a simultaneous BRAF-I treatment could even improve BM destruction by a very focal radiation therapy.

Figure 1. Time to new brain metastasis and overall survival in the 24 patients who underwent GKRS under BRAF-I. (A) Time to new brain metastasis from first GKRS under BRAF-I. (B) Overall survival from first GKRS under BRAF-I. (C) Overall survival from first dose of BRAF-I.
like SRS, without actually increasing adverse events, thus being of benefit for the patient.

It is likely that there are two different situations as to what we should do in practice when patients are requiring radiotherapy. On the one hand, there is no evidence that BRAF-I should be interrupted for GKRS or other techniques of SRS. On the other hand, a transient discontinuation may be cautiously advised for other radiation therapies including WBRT. However, we do not have data about how long BRAF-I interruption should be to ensure safety of a radiotherapy procedure. Twice the half-life of the BRAF-I, i.e. 2 × 5 days for vemurafenib, and 2 × 1 day for Dabrafenib before and after radiotherapy has been proposed, without any certainty that it would be enough and no reason to think that it could affect in any way on radiation recall.

Various series using GKRS in MM patients reported BM control rates between 73% and 90% with short-term local control upper 98% at 3 months [2, 3, 18–21] and on-demand use of possibly repeated GKRS is of benefit for the patient [2, 21]. In the present series, a median OS of 48.8 weeks from first dose of BRAF-I, with a 6-month survival of 78.8%, and a 12.9-week median time to new BM after first GKRS provide some indicators. No conclusion can be drawn about the efficacy of the combination and a possible preventive effect of BRAF-I on the development of new BMs, for lack of controls. However, at least our data do not suggest that an abnormal radiotoxicity could seriously alter prognosis. Indeed, the BREAK-MB study using BRAF-I alone (Dabrafenib) showed a median OS of 33 and 31 weeks, in the first-line cohort and in the previously treated BM cohort, respectively, with 6-month survival estimate of 61.1% [6]. Whether or not combining GKRS on demand with MAP kinase inhibitors is really a benefit for the patient remains to be tested prospectively. This potential benefit is further supported by a preservation of the neurological status, since only 6 of our 30 patients developed neurologic symptoms along their entire disease course.

**Conclusion**

The combination of GKRS and BRAF-I appears safe for BM in MM patients. GKRS can thus be safely used and repeated on demand as needed in patients under BRAF. The interruption of the BRAF-I seems useless with techniques of SRS although it may be still advised in usual radiation therapy procedures. The rather good figures of patient survival in this series suggest that it would be interesting to assess how much local control of BM by SRS can prolong patient comfort and survival in BRAF-I-treated patients, or either the potential adjuvant protective effect of BRAF-I against new BM, after the treatment of isolated BM by SRS.

**Disclosure**

The authors have declared no conflicts of interest.

**References**