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Original Research

Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery

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Abstract ***Background:*** Targeted therapy (TT) and immunotherapies (ITs) have dramatically improved survival in metastatic melanoma (MM). However, their efficacy on brain metastasis (BM) remains limited and poorly documented.
Patients and methods: Retrospective cohort of consecutive MM patients (pts) with BMs, all systematically upfront treated by Gamma-Knife (GK) at first BM and retreated in case of new BMs, from 2010 to 2015 at the time when ipilimumab BRAF ± MEK inhibitors and anti-PD1 were introduced in practice. Survival after 1st GK (OS_{GK1}) according to prognostic factors and treatment.
Results: Among 179 consecutive pts treated by GK, 109 received IT and/or TT after the 1st GK. Median OS_{GK1} was 10.95 months and 1- and 2-year survival rates were 49.5% and 27.4%, respectively, versus a median overall survival (OS) of 2.29 months ($p < .001$) in those who did not receive IT or TT. In pts who initially had a single BM, median OS and 1- and 2-year survival rates were 14.46 months, 66.7% and 43.4%, respectively; in pts with 2–3 BMs: 8.85 months, 46.4% and 31%, respectively; in pts with >3 BMs: 7.25 months, 37.2% and 11.9%, respectively. Multivariate analysis for OS_{GK1} confirmed that IT and TT were significantly and highly protective. Best OS_{GK1} was observed in BRAF–wild-type pts receiving

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anti-PD1 or in BRAF-mutated pts receiving BRAF-inhibitors and anti-PD1 (12.26 and 14.82 months, respectively).
Conclusion: In real-life MM pts with BMs, a strategy aiming at controlling BM with GK together with TT and/or TT seems to achieve unprecedented survival rates.

1. Introduction

Targeted and immune treatments have dramatically improved the course of metastatic melanoma (MM); however, patients (pts) with brain metastases (BMs) still carry a poor prognosis [1]. Despite similar response rate in BMs as in extra-cerebral sites, the impact of BRAF-inhibitors (BRAF-inh) on progression-free survival and overall survival (OS) seems much lower than in pts without BMs [2,3]. Similarly, although BMs can respond to immunotherapy (IT), they are a difficult target for ipilimumab [4], and few data are available for anti-PD1 [5,6,7]. Stereotactic radiosurgery (SRS) with Gamma-Knife (GK) is used to control BMs in different cancers, providing both a survival and functional benefit [8]. SRS was initially performed only once in pts with a maximal number of three BMs. Many centres have now adopted an 'on-demand' strategy (GK_{OD}), which can address as many BMs as required and can be repeated during follow-up when new BMs develop (Fig. 1) [8–10].

Combining an upfront and repeated direct control of BMs by SRS and a systemic treatment with targeted therapies (TT) or IT, is a way to keep BMs under control and avoid the occurrence of life-threatening situations or impairment of neurological function. Meanwhile, IT or TT control extra-cerebral disease and hopefully prevent new BMs. Furthermore, there may be a real synergy between radiation and IT [11–13], and no deleterious effect when combining GK with BRAF-inh [14].

In the present paper, we analyse the survival in a large retrospective cohort of MM pts, whose BMs were systematically treated by GK_{OD} as soon as they were detected at the time of the introduction of TT and checkpoint blockers in our practice.

2. Methods

2.1. Population

All pts with BMs treated in our department (La Timone, Marseille, France) by a standardised strategy of GK_{OD} from the period of March 2010 to November 2015 were included, independently of the medical treatment they received thereafter. First GK was systematically performed as soon as 1st BM was diagnosed and repeated as many times and for as many BMs as required

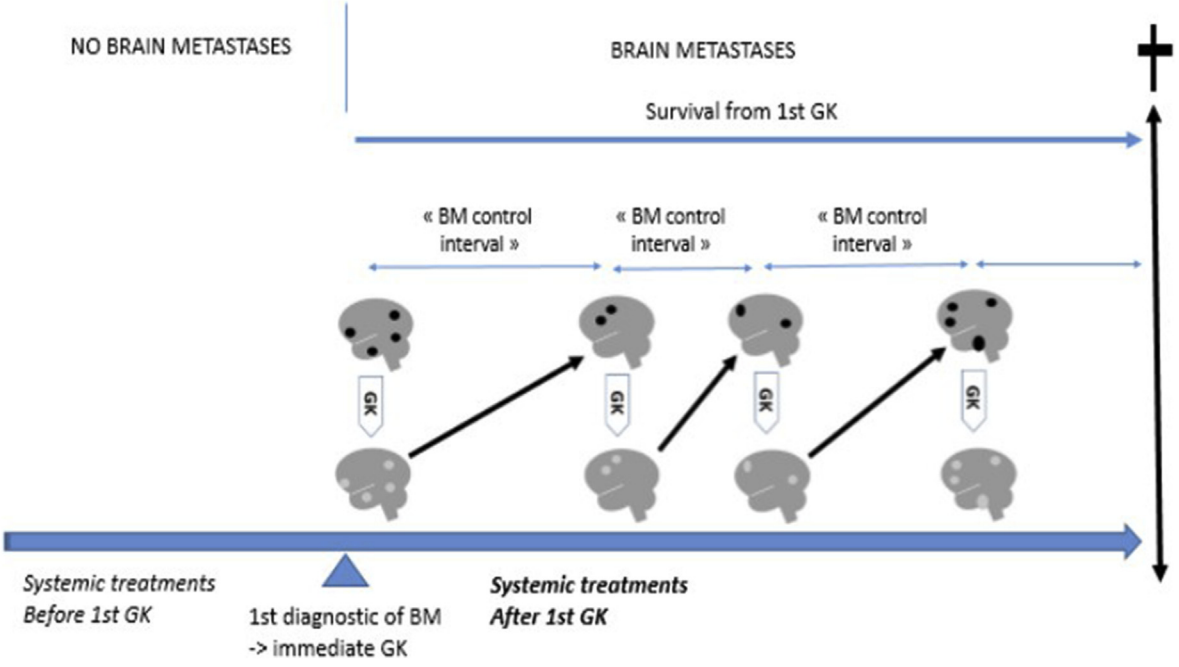

Fig. 1. Strategy of Gamma-knife (GK) on demand. BM, brain metastasis.