European Journal of Cancer 75 (2017) 169–178

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies

Ee Siang Choong [a], Serigne Lo [b], Martin Drummond [b], Gerald B. Fogarty [b,d,e], Alexander M. Menzies [b,e,f], Alexander Guminski [b,e,f], Brindha Shivalingam [b,c,e], Kathryn Clarke [d], Georgina V. Long [b,e,f], Angela M. Hong [b,d,e,*]

[a] *Chris O Brien Lifehouse, Camperdown, NSW, Australia*
[b] *Melanoma Institute Australia, The University of Sydney, NSW, Australia*
[c] *Royal Prince Alfred Hospital, Camperdown, NSW Australia*
[d] *Genesis Cancer Care, Mater Radiation Oncology, North Sydney, Australia*
[e] *Mater Hospital, North Sydney NSW, Australia*
[f] *Royal North Shore Hospital, St Leonards, NSW, Australia*

Received 18 October 2016; received in revised form 4 January 2017; accepted 11 January 2017
Available online 23 February 2017

KEYWORDS
Melanoma;
Stereotactic radiosurgery;
Brain metastasis;
Anti-PD-1 antibody;
Immunotherapy;
Targeted therapy;
BRAF inhibitors

Abstract ***Introduction:*** With new systemic therapies demonstrating activity in melanoma brain metastasis, most of the previously reported stereotactic radiosurgery (SRS) data are superseded. In this study, we report the outcomes (overall survival [OS] and brain control [BC]) and identify factors that associate with such outcomes in the era of modern systemic therapy.
Method: A total of 108 patients treated with SRS from 2010 to 2015 were included. Systemic treatment use within 6 weeks of SRS was noted. OS was defined as time from SRS to death or last follow-up, and BC was defined as absence of any active intracranial disease during follow-up. Univariate and multivariate Cox proportional hazard analyses were performed on clinicopathological prognostic features associated with OS and BC.
Results: The median age was 64.3 years, and the median follow-up was 8.6 months. Seventy-nine (73.1%) patients received systemic treatment. The median OS were as follows: anti-CTLA4 – 7.5 months (95% CI: 4.4–15.6), anti-PD1 – 20.4 months (95% CI: 8.8 – N/A) and BRAF inhibitor (BRAFi) ± MEK inhibitor (MEKi) – 17.8 months (95% CI: 11.8 – N/A). Median BC was as follows: anti-CTLA4 – 7.5 months (95% CI: 4.0–15.6), anti-PD1 – 12.7 months (95% CI: 5.5 – N/A) and BRAFi ± MEKi – 12.7 months (95% CI: 8.3–18.5). In multivariate analysis, age and type of systemic therapy were strongly

* *Corresponding author*: Melanoma Institute Australia, 40 Rocklands Road, North Sydney, NSW 2060, Australia. Fax: +61 2 9954 9418.
E-mail address: angela.hong@sydney.edu.au (A.M. Hong).

http://dx.doi.org/10.1016/j.ejca.2017.01.007

associated with OS. Age, Eastern Cooperative Oncology Group performance status, Graded Prognostic Assessment (GPA) score, and presence of symptoms were associated with BC.
Conclusions: Favourable outcomes are seen in patients treated with SRS and with the best survival seen in patients treated with anti-PD1. Known independent prognostic factors for survival such as age and performance status and GPA score remain relevant in this setting.

1. Introduction

Development of melanoma brain metastasis (MBM) is common in patients with stage 4 melanoma, and it is often devastating, resulting in significant neurological symptoms and reduction in quality of life. Historically, survival varies according to many factors including the local treatment received; 8.9 months for surgery plus whole brain radiation therapy (WBRT), 8.7 months for surgery alone, 3.4 months for WBRT alone, and 2.1 months for supportive care alone [1,2]. Increasingly, stereotactic radiosurgery (SRS) is used in the management of MBM with excellent local control rate of up to 90% and an associated median survival of 5–11 months [3,4].

In recent years, the number of effective systemic drug options for patients with metastatic melanoma has rapidly expanded with immune checkpoint inhibitors and targeted agents for V600 BRAF mutated melanoma. These modern systemic therapies have demonstrated superiority compared to conventional cytotoxic chemotherapy with higher response rates and improved progression free and overall survival (OS) in both pretreated and treatment naïve patients with metastatic melanoma [5–13]. Unlike chemotherapy, these drugs have also demonstrated activity in MBM. Ipilimumab has shown activity against MBM that is similar to that seen in extracranial disease, with some patients experiencing long term responses [14–18]. Early analysis from a small single institution open label phase 2 study has demonstrated that anti-PD1 inhibitors have activity in MBM [19]. Targeted agents of the mitogen activated protein kinase (MAPK) pathway including BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi) have also demonstrated activity in MBM in a multi-centre phase 2 and retrospective series [20–22], and the clinical trial of the combination is fully recruited (NCT02039947).

With such changes in systemic drug therapy, management of MBMs has become more complex [23]. In this study, we sought to report the clinical outcomes and factors associated with outcomes in patients with MBM who received SRS in the era of effective systemic drug therapies.

2. Materials/methods

A retrospective review of patients who received SRS for MBM from August 2010 to December 2015 at the Melanoma Institute Australia was conducted following ethics board approval. Clinico-pathological information and follow-up status of all patients were extracted from the Melanoma Research Database, a prospective research database of the Melanoma Institute Australia. In particular, patients who received either immunotherapy or a MAPK pathway inhibitor within 6 weeks, before or after, SRS were recorded. Patients who had prior surgery and WBRT were included. SRS was delivered using either a LINAC-based or Gamma-knife approach. The cumulative volume of brain metastasis was calculated from the SRS planning system. Graded Prognostic Assessment (GPA) and Disease-specific GPA (DS-GPA) scores were calculated [24,25].

3. Endpoints and statistical analysis

Patients were followed clinically with the treating clinician at 3-weekly to 3-monthly intervals. MRI of the brain and CT and/or PET of the body were performed every 3 months. Endpoints evaluated were OS, defined as time from SRS to death, and brain control (BC), defined as absence of any active intracranial disease (new lesion or progression of existing lesion) on clinical and radiological evaluation during follow-up. Patients who did not experience the outcome are censored at their last follow-up date.

Univariate and multivariate Cox proportional hazard regression were performed on prognostic features associated with OS and BC. Variables in the multivariate models were introduced by means of purposeful selection of variables method. Variables with a univariate relatively moderate association (P-value < 0.25) were included in a full model and then stepwise dropped until all remaining variables are significant at 5% level.

4. Results

4.1. Patient characteristics

A total of 108 patients who received SRS to a total of 339 lesions in the study period were identified (Table 1). The median age was 64.3 years, and 75 (69.5%) were males. The median follow-up was 8.6 months (range 0.4–39.6). Nine (8.3%) patients had MBM only as the first presentation of metastatic melanoma. Sixty (55.6%)