



Fluorescence image-guided surgery and repetitive Photodynamic Therapy in brain metastatic malignant melanoma

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KEYWORDS

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Summary Metastatic brain melanoma occurs in about 3.5% of patients suffering from malignant melanoma. It has disabling effects on cognition, memory, language and mobility. We studied the use of fluorescence image-guided resection and repetitive Photodynamic Therapy in six consecutive metastatic brain melanomas. Three were males and the mean age of the group was 52.8 years.

Results: All six patients (100%) remained free of brain disease till death, 50% died of malignant melanoma elsewhere, and 50% died of unrelated causes.

Conclusion: Adjuvant fluorescence image-guided resection and repetitive Photodynamic Therapy offers an excellent local control of metastatic brain melanoma.

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Introduction

Brain metastases are the most common form of malignant brain tumours. They have disabling effects on cognition, memory, language, and mobility and are an enormous toll for patients, their families and society. Brain metastases have an incidence of 12 per 100,000 per year and 15–40% of systemic cancers metastasize to brain [1]. In a recent study of 729 patients with brain metastases, malignant melanoma was the primary tumour in 80 patients (11%) [1], and 25 patients (3.5%) developed metastatic brain melanoma (MBM) out of 700 melanoma patients [2]. Patients with MBM may present with headaches (40–50%) usually worse on

bending or straining, with seizures (10–20%), cerebrovascular accident-like symptoms (5–10%), focal neurologic deficits or cognitive dysfunction. MBM is also more likely to bleed than other types of brain metastases.

The prognosis of patients affected by MBM depends on the extent of medical intervention. With supportive therapy alone the survival is 3–8 weeks and survival can be extended to 9–22 weeks with whole brain radiotherapy [2,3]. Currently MBM are treated with a combination of surgery, radiotherapy and chemotherapy. However, the survival of MBM is merely 26 weeks [3]. Good prognostic factors include Karnofsky Performance Status (KPS) more than 70, controlled primary extracranial disease, no extracranial sites of metastases, and age less than 65 [4]. The goals of treatment are to prevent or relieve neurologic symptoms, improve the quality of remaining life and extend life if possible. Therefore, there still a long way to go to improve survival of patients who develop MBM. We explored the use of fluorescence image-guided surgical resection (FIGS) and repetitive

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Table 1 Summary of six melanoma brain metastases treated with repetitive PDT.

Patient number	Age (years)	Sex	Survival in weeks	Cause of death
1	81	Male	9	Unrelated cause
2	52	Female	70	Other metastasis
3	26	Female	70	Unrelated cause
4	51	Male	30	Unrelated cause
5	57	Female	13	Other metastasis
6	50	Male	17	Other metastasis
Total 6	Mean 52.8	3F:3M	Mean 33.83	No brain recurrence

Photodynamic Therapy (rPDT) in addition to conventional therapy in a series of six consecutive MBM patients.

Methods

All patients agreed to participate in the study gave informed consent. They received 2 mg/kg body weight Photofrin® (Axcan Pharma, Quebec, Canada) intravenously 48 h before surgery. On the day of surgery, they were also given 20 mg/kg body weight 5-aminolevulinic acid (ALA, medac, Hamburg, Germany) mixed in non-fizzy orange juice orally 3 h before surgery. The surgical microscope and image-guided system was used to locate and remove the bulk of the tumour with intraoperative neuronavigation and the rest of the tumour was removed using fluorescence-guided resection (FGR) followed by repetitive Photodynamic Therapy. The FIGS and rPDT techniques were described in detail previously by the senior author [5,6]. In brief rPDT was given intra-cavity using balloon diffuser inflated to fill the surgical cavity with 0.32% Intralipid and the light was delivered using Diode Laser 630 nm (Biomed, Cambridge, UK). The total dose of rPDT was 500 J/cm² given on five consecutive days. The median total light dose was 394.91 J per day (range from 142.2 J to 774 J per day). All patients received dexamthazone 4 mg/kg Qid and ranitidine 150 mg BD few days before treatment and continued for 24 h after rPDT was finished. Thereafter the steroids were tapered gradually and patients were followed up clinically and radiologically every three months till death. We have not used antiepileptic therapy prophylactically and none of our patients developed seizures.

Photoprotection

All patients took satisfactory protection from direct sun exposure through the use of rimmed hats, sunglasses, gloves, long sleeves and trousers.

Patients

In this study 6 MBM patients were recruited. Their mean age was 52.8 years with a male to female ratio of 1.

Results

All six (100%) patients remained free of brain disease at the time of their death. Three patients (50%) died of malignant melanoma metastases elsewhere in the body. The other

three patients (50%) died of unrelated causes. The median survival was 50 weeks and the average survival was 34.8 weeks (Table 1). Five patients demonstrated fluorescence during surgery. There were two post operative complications during this study: one patient developed DVT that was treated successfully without any long term effects and one patient developed fracture of the balloon catheter after four treatments requiring surgical extraction. There were no surgical deaths, neurological deficits or infections.

Discussion

FGR and PDT are safe and well tolerated treatments that appear to give survival benefits in patients with malignant brain tumours [5,6]. FGR was reported to significantly increase the completeness of tumours excision and improve significantly time to tumour relapse in malignant gliomas in two prospective randomized controlled studies recently [5,7]. Furthermore, the addition of rPDT had improved survival and time to tumour relapse in malignant gliomas [5]. Earlier studies concentrated on PDT in malignant gliomas without FGR. Two of these studies included one MBM each in their series. Powers et al. [8] reported a single case out of seven malignant brain tumours treated with PDT and the MBM progressed despite PDT. Kostron et al. [9] reported another patient with 4 years history of metastasing MBM treated with no information about the outcome of therapy as the study was reporting the affects of PDT on primary malignant gliomas. Our study constitutes the biggest series in the literature of PDT in MBM and the only study that explored the use of FGR and rPDT in MBM. It had demonstrated a very high local control rate of MBM. MBM had been shown to take up Photofrin previously [8]. Powers et al. [8] found the concentration of Photofrin to be 9.9 ng/mg of MBM tissue and five out of six of our patients fluoresced during FGR, indicating that MBM preferentially takes up and retains the photosensitizers.

Conclusion

Adjuvant FIGS and rPDT offer excellent local control of metastatic brain melanoma and warrants further studies.

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