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Clinical Study

Recurrent glioblastoma: Current patterns of care in an Australian population

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ABSTRACT

This retrospective population-based survey examined current patterns of care for patients with recurrent glioblastoma (rGBM) who had previously undergone surgery and post-operative therapy at original diagnosis. The patients were identified from the Victorian Cancer Registry (VCR) from 2006 to 2008. Patient demographics, tumour characteristics and oncological management were extracted using a standardised survey by the treating clinicians/VCR staff and results analysed by the VCR. Kaplan–Meier estimates of overall survival (OS) at diagnosis and progression were calculated. A total of 95 patients (48%) received treatment for first recurrence; craniotomy and post-operative treatment (38), craniotomy only (34) and non-surgical treatment (23). Patients receiving treatment at first progression had a higher median OS than those who did not (7 *versus* 3 months, $p < 0.0001$). All patients progressed after treatment for first progression with 43 patients (45%) receiving treatment at second progression. To our knowledge this is the first population-based pattern of care survey of treatment for rGBM in an era where post-operative "Stupp" chemo-radiation is standard. First and second line therapy for rGBM is common and associated with significant benefit. Treatment generally includes re-resection and/or systemic therapy.

1. Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumour in adults [1]. Despite aggressive multimodal treatment, GBM is associated with a poor prognosis, with a median survival of just under 15 months [2]. For suitable patients, post-operative concurrent radiation and temozolomide followed by 6 months of temozolomide became the standard of care worldwide after publication of the pivotal EORTC 26981/NCIC-CE3 study showing a survival benefit with the addition of temozolomide to radiation [2]. This survival benefit has also been demonstrated in population-based studies [3–6]. Indeed, our own data, demonstrated early uptake of this new treatment approach in our Australian patient population and documented a significant survival benefit against our historical control [3].

In contrast to *de novo* GBM, there is no standard of care in the management of recurrent glioblastoma (rGBM) and no treatment has been shown to definitively improve outcomes. Options include re-resection, re-irradiation and systemic therapies such as chemotherapy, bevacizumab and clinical trials. However, there is a paucity of large prospective randomised studies to support their use. Certainly, more recent studies have been disappointing with a number of newer systemic drugs showing no benefit over older chemotherapy drugs such as lomustine. In general, for patients with rGBM receiving systemic therapies, the 6 month progression free survival and median overall survival (OS) is 13–43.8% and 5.1–13 months respectively [7–12]. To our knowledge there are no prospective randomised studies of re-resection or re-irradiation for rGBM. In carefully selected patients undergoing

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re-resection for rGBM the median OS is reported as 7.4–19 months [13–17] and across a variety of radiotherapy techniques the median OS is reported as between 8–13 months [15,18–21].

We have previously reported the overall results on patient outcomes in a population based survey [3,22]. We now examine the patterns of care for the sub-group of patients with rGBM who had undergone standard post-surgery concurrent radiation and chemotherapy.

2. Methods

2.1. Questionnaire and data collection

The methodology has been previously reported by Gan et al. [3]. A population-based sample of all adult patients ($\geqslant$18 years) with histologically confirmed GBM (*International Classification of Diseases* codes 710–718) diagnosed in Victoria, Australia between 1 January 2006 and 31 December 2008 inclusive were identified from the Victorian Cancer Registry (VCR). The VCR is a state-wide registry, which receives notification of all diagnoses of cancer within Victoria, representing approximately one quarter of the Australian population [23]. Eligible patients were residents in the state of Victoria with a new histologically confirmed diagnosis of GBM.

Treating clinicians were identified by registry staff and sent a questionnaire relating to the management of each patient. The questionnaire was based on that used previously [22,24,25] and updated by a multi-disciplinary steering committee comprised of neurosurgeons, radiation oncologists, neurologists and medical oncologists with expertise in managing GBM. The questionnaire obtained the following data: patient demographics, histological characteristics, referral patterns, treatment characteristics (including surgery, radiotherapy and chemotherapy), relapse patterns and treatment. The histological results shown are based on the primary pathology report for each patient. Detailed data regarding symptoms and diagnostic imaging was not collected. All clinicians involved in each patient's care were contacted directly to complete the relevant questionnaires. Three weeks after the initial approach, VCR staff contacted each non-responding clinician and offered assistance with the completion of the questionnaire. All data was subsequently de-identified and checked by VCR staff. Completed and checked questionnaires were then coded and computerised before statistical analysis by the VCR statistician. Kaplan–Meier estimates of OS from diagnosis and from first progression were calculated and compared using the log-rank test where p values of $\leqslant$ 0.05 were considered significant. All analyses were carried out using the Statistical Package for the Social Sciences version 20 (IBM, Armonk, NY, USA).

2.2. Ethical approval

The Cancer Council of Victoria Institutional Ethics Committee approved the study.

3. Results

3.1. Treatment at initial diagnosis from 2006–2008

The demographics of this cohort during first-line treatment have been described by Gan et al. [3]. In summary, 351 patients with *de novo* GBM were reviewed, with the majority of patients being male (62%) and at a mean age of 64 years. The median follow up was 12.2 months. Of these 351 newly diagnosed cases, 243 patients (69%) received post-operative treatment. Ultimately, 196 patients (81%) of these 243 patients experienced disease progression at a median of 7.0 months after their initial diagnosis. The remaining 19% had not progressed at the time of this study. Data about treatment at first or subsequence recurrence was available for 194 patients, with missing information for the other two patients.

3.2. Treatment at first progression

At the time of their first disease progression, 95 of the 194 patients (49%) received further therapy (Fig. 1). Clinical characteristics for patients that received treatment compared to those that did not receive treatment on first recurrence is presented in Table 1. There were no clear differences between the two groups. Compared to the 1998–2000 period [22] there was a small but significant increase in rates of treatment at first progression in 2006–2008 (48% *versus* 42% respectively, $p < 0.001$). Patients from regional Victoria were less likely to receive treatment at first progression compared to patients living in the metropolitan area, 27% *versus* 73% respectively, which approached statistical significance ($p = 0.064$).

Of the 95 patients who received treatment at first progression, 72 patients (76%) underwent re-resection of whom 35 patients (48%) underwent re-resection followed by post-operative chemotherapy, including carmustine (14%), carboplatin (30%), combination carboplatin and etoposide (3%) and a variety of temozolomide schedules (46%). One patient (3%) was treated with post-operative radiotherapy and two patients received concurrent chemoradiation post-resection. Of the patients who received post-operative chemotherapy, three patients (8%) were enrolled on trials of novel systemic agents (Table 2).

Twenty-three patients (24%) received non-surgical treatment at first progression, of whom 19 (79%) received chemotherapy including temozolomide, carmustine, carboplatin and high dose tamoxifen (Table 2). Of those who received chemotherapy one patient received bevacizumab in combination with carboplatin and one patient was enrolled onto a clinical trial. Two patients received high dose tamoxifen and two were treated with re-irradiation only.

Patients who received treatment on first progression had a median OS of 7 months (95% confidence interval [CI] 7.56–11.08), compared to those who did not receive any treatment who had a survival of 3 months (95% CI 3.26–5.19) ($p < 0.0001$, log-rank test) (Fig. 2a). The impact of different treatment approaches at progression was examined. Patients who received chemotherapy for first progression had the highest survival (10 months, 95% CI 4.9–15.1) followed by patients who had chemotherapy after surgery (8.0 months, 95% CI 6.4–9.6). Patients who underwent craniotomy alone had a survival of 5.0 months (95% CI 3.1–6.9). None of these differences reached statistical significance (Fig. 2b).

3.3. Treatment at second progression

All 95 patients treated at first progression developed recurrent disease. Of the 95 patients, 52 patients (55%) received no further therapy at second progression. No difference was seen in age or sex between patients who received second line therapy and those who did not (Table 2). Patients from regional Victoria were again less likely to receive second line therapy as compared to patients living in the metropolitan area, 35% *versus* 65%, which approached statistical significance ($p = 0.051$).

Treatment at first progression strongly influenced treatment at second progression. Forty-three (45%) patients were treated at second progression with a variety of systemic agents including bevacizumab, carboplatin, carmustine, etoposide, high-dose tamoxifen, irinotecan, pegylated liposomal doxorubicin, procarbazine, and temozolomide. One patient was enrolled into a clinical trial. As