Effect of temozolomide on central nervous system relapse in patients with advanced melanoma


Cancer Research UK Department of Medical Oncology, Christie Hospital NHS Trust, Manchester, UK. Tel: 0161 226052; Fax: 0161 226179; email: M.Middleton@icrf.icnet.uk (M. J. Paul, Y. Summers, N. Thatcher, M. R. Middleton). Cancer Research Unit, The Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne, UK (A. H. Calvert). Cancer Treatment Centre, Mount Vernon Hospital, Northwood, Middlesex, UK (G. Rustin). Cancer Research UK Data Centre, Regent’s Park, London, UK (M. H. Brampton).

Temozolomide has shown efficacy in the treatment of metastatic melanoma similar to that of dacarbazine (DTIC), the standard chemotherapy, but with the added benefit of penetration into the central nervous system (CNS). Isolated CNS relapse is increasingly a problem for patients who respond to biochemotherapy. By replacing DTIC with temozolomide in treatment regimens, the incidence of CNS relapse might be reduced. This hypothesis is difficult to test in a prospective randomized controlled trial because of the large number of patients that would be required. We have examined this question in a retrospective case control study, observing the rates of CNS relapse in advanced metastatic melanoma patients responding to DTIC- or temozolomide-based chemotherapy in three institutions. Twenty-one DTIC and 20 temozolomide responders were identified, and have been followed up for a median of 19.0 months (range 6.0–74.3 months). CNS relapse occurred in nine DTIC- and two temozolomide-treated patients, a statistically significant difference in favour of the new agent ($P = 0.03$). These results support the investigation of temozolomide as a replacement for DTIC in systemic treatment regimens for melanoma. © 2002 Lippincott Williams & Wilkins

Key words: Brain metastasis, dacarbazine, melanoma, relapse, temozolomide

Introduction

The prognosis for patients with advanced metastatic melanoma remains poor, with less than 20% of patients responding to dacarbazine (DTIC), the standard chemotherapy.¹ Such responses are usually confined to patients with soft tissue or pulmonary disease, are short lived and do not impact on overall median survival. Combination chemotherapy has not improved on these results,²,³ but combinations of cytokines and chemotherapy appear to hold some promise. Phase II trials with such regimens report objective response rates of 40–50%, with complete responses in up to one sixth of patients, half of whom survive long term.⁴—⁶ Although this approach has yet to be tested in phase III trials, it has become apparent that central nervous system (CNS) relapse is an important cause of treatment failure in responding patients. Up to half of these patients develop CNS disease, often as the only site of relapse, and this is almost always fatal.⁷

Temozolomide is a novel oral alkylating agent that has demonstrated efficacy similar to that of DTIC against advanced extracranial metastatic melanoma.⁸ Unlike DTIC, temozolomide does not require hepatic activation to form the active intermediary 5-(3-methyl-1-trazeno)imidazole-4-carboxamide (MTIC), which is produced by spontaneous chemical conversion.⁹ Temozolomide crosses the blood–brain barrier¹⁰ and has been shown to have activity against primary brain tumours and CNS melanoma metastases.¹¹,¹² To date, DTIC has shown no such activity against CNS disease, presumably because it is only converted into the active metabolite in the liver, and the metabolite penetrates the CNS poorly.¹³ This has led to the hypothesis that replacing DTIC with temozolomide in biochemotherapy regimens might reduce the incidence of CNS relapse amongst responding patients, which might in turn lead to an increase in the number of long-term survivors.
Even if the response rates reported in phase II studies were maintained, a prospective study to test this hypothesis would be difficult to achieve. An adequately powered randomized control trial would need several hundred patients to detect even a 25% change in relapse rates. We have therefore used the data from the early Cancer Research Campaign (CRC) phase II trials of temozolomide to construct a retrospective case control study to test the hypothesis.

**Materials and methods**

**Patients**

Patients were selected from those undergoing chemotherapy for melanoma in the three leading centres taking part in the CRC clinical trials programme for temozolomide. DTIC-treated controls were drawn from a contemporaneous study at the Christie Hospital. Temozolomide-treated patients were drawn from three phase II studies. The entry criteria for the four studies were similar. The results of these trials have all been published elsewhere.12,14,15 Patients were included in the analysis provided that they had stage IV disease, with no clinical evidence of CNS involvement, at the start of treatment and achieved an objective response with chemotherapy according to World Health Organization (WHO) criteria.16 Brain scans were not required prior to study entry unless there were symptoms suggestive of intracranial disease. Details of the patients' treatment and follow-up were extracted from the CRC database. All the patients were reviewed regularly, and follow-up did not differ according to the treatment received. Individual case notes were then examined to determine whether and when they had suffered CNS relapse.

**Treatment**

Temozolomide-treated patients received five 200 mg/m² doses of drug, repeated every 28 days, or 150 mg/m² if they had received prior chemotherapy. Doses were delivered once daily or 4 hourly depending on the trial in which the patient took part. Patients receiving DTIC were treated with a single dose of 800 mg/m² every 3 weeks, along with 9 MIU interferon-α2a three times a week, or 220 mg/m² on days 1–3 of each 3 week cycle as part of the Dartmouth regimen (i.e. with carmustine [BCNU] 150 mg/m² every other cycle, cisplatin 25 mg/m² daily on days 1–3 and tamoxifen 40 mg daily).

**Statistical analysis**

CNS relapse was defined as the development of symptoms consistent with the diagnosis that could not otherwise be explained. Although it was deemed preferable that radiological confirmation be sought, this was not a requirement. Kaplan–Meier plots were constructed for overall survival and for CNS relapse, comparisons being made using the log-rank test.

**Results**

Twenty patients were identified as responding to temozolomide and 21 to DTIC. The patient characteristics are listed in Table 1. Patients have been followed up for a median of 19 months (range 6.0–74.3 months). During this period only two patients from the temozolomide-treated group developed CNS disease compared with nine in the DTIC-treated group (Figure 1). All the relapses save one, in a DTIC-treated patient, were confirmed radiologically. Despite the small number of patients, this result was statistically significant (P = 0.03). Seven of the DTIC-treated patients remain alive compared with six from the temozolomide-treated group. All of the patients with CNS relapse have died, surviving a median of 61 days from the diagnosis of relapse (range 24–381 days).

**Discussion**

We have found that patients responding to temozolomide chemotherapy are less likely to develop CNS metastases than those treated with DTIC-based regimens.
mens. The lower incidence of CNS relapse amongst patients treated with temozolomide suggests that it may be effective in treating minimal residual disease at this site, by virtue of its ability to penetrate the blood–brain barrier. The substitution of temozolomide for DTIC in biochemotherapy regimens could therefore be expected to lead to a reduction in the overall incidence of treatment failure in responding patients, since the CNS is frequently the only site of relapse.

There are a number of limitations to this study: it is retrospective but case-controlled, the patient numbers are relatively small, and the population studied received chemotherapy rather than biochemotherapy. Given this, and since brain magnetic resonance imaging was not routinely performed in these studies, it could be that the difference observed is due to a difference in baseline characteristics between the two groups. It will be important to evaluate the outcomes of biochemotherapy regimens that include temozolomide to test our hypothesis further. A number of investigators have instigated trials with such regimens, most of which have analogous DTIC-based counterparts. It will therefore be possible to determine whether our observations are reproduced with biochemotherapy.

In common with previous reports, survival in our responding patients was relatively short, but was significantly longer in the DTIC-treated group. The median duration of responses to chemotherapy in melanoma is about 6 months, as we observed in the temozolomide-treated patients, but the DTIC respon-

ders relapsed a median of 10 months after therapy began. Due to the small number of patients, the differences in overall survival and response duration observed were not statistically significant (\( P = 0.6 \) and 0.3, respectively). Nevertheless, it is possible that temozolomide did not prevent CNS relapse, merely delayed its manifestation sufficiently so that patients died of their extracranial disease. However, we found that four of the 11 patients who survived at least 2 years after DTIC treatment developed CNS melanoma as opposed to only one of six such temozolomide-treated patients. A delay in the development of overt CNS disease would be valuable in these patients, even if it does not affect survival, since quality of life declines dramatically with the advent of brain metastases.

If true, our hypothesis is only of interest if the results seen with biochemotherapy to date are reproduced in phase III trials. Although encouraging, the response rates achieved so far are similar to those with the Dartmouth regimen in phase II studies, and these were not reproduced in phase III trials and were not associated with any survival benefit. Only one randomized study comparing chemotherapy and biochemotherapy has been reported in full to date. Rosenberg and colleagues published results from 102 patients randomized to receive cisplatin, DTIC and tamoxifen with or without interleukin-2 and interferon-\( \alpha \). The response rate with biochemotherapy was (non-significantly) higher (44% versus 27%), but there was a trend towards improved survival with chemotherapy alone (median of 15.8 months versus 10.7 months). However, the median survival of the chemotherapy-treated patients in this trial is longer than is usually reported. As yet, randomized controlled trial evidence for improved efficacy with biochemotherapy is lacking, but trials to address this are in progress, and one of the largest recently showed a trend towards improved survival with biochemotherapy on interim analysis.

In conclusion, we have demonstrated a possible role for temozolomide in preventing CNS relapses in patients responding to systemic therapy. Further work is required to confirm this observation, and to establish the role of biochemotherapy in the management of advanced metastatic melanoma.

Acknowledgements

This work was supported in part by the Cancer Research Campaign. We are grateful to David Ryder...
at the Christie Hospital, Manchester, for help with the statistical analysis.

References


(Received 9 May 2001; accepted in revised form 23 July 2001)