Temozolomide in Combination with Interferon α-2b in Patients with Metastatic Melanoma

A Phase I Dose-Escalation Study

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BACKGROUND. Metastatic melanoma (MM) is associated with a high risk of central nervous system (CNS) metastases, and current chemotherapy does not adequately treat or protect patients with MM against CNS metastases. Therefore, the authors initiated a Phase I study to determine the pharmacokinetics and safety profile of temozolomide (TMZ), a novel oral alkylating agent known to cross the blood-brain barrier, in combination with interferon α-2b (IFN-α2b).

METHODS. Twenty-three patients with MM were enrolled in this single-center, open-label study. Patients with CNS metastasis were excluded. One cohort (n = 6 patients) received oral TMZ (200 mg/m^2 per day) for 5 days every 28-day cycle plus subcutaneous IFN-α2b (5 million International Units [MIU]/m^2 per day, 3 times per week). A second cohort (n = 17 patients) received TMZ 150 mg/m^2 per day on the same schedule plus escalating doses of IFN-α2b (5.0 MIU/m^2 per day, 7.5 MIU/m^2 per day, and 10 MIU/m^2 per day 3 times per week).

RESULTS. The most common adverse events were fatigue, fever, nausea/emesis, anxiety, and diarrhea. Most toxicity was mild to moderate in severity. The primary dose-limiting toxicity was thrombocytopenia. The maximum tolerated dose was either TMZ 150 mg/m^2 plus IFN-α2b 7.5 MIU/m^2 or TMZ 200 mg/m^2 plus IFN-α2b 5.0 MIU/m^2. Four patients (17%) had objective responses (one complete response and three partial responses), and four patients had stable disease. The median survival was 9 months. The pharmacokinetics of TMZ were not affected by coadministration of IFN-α2b.

CONCLUSIONS. TMZ can be combined safely with IFN-α2b. This regimen demonstrated clinical activity in patients with MM and merits further investigation to define its effect on the incidence of brain metastases. ***Cancer*** **2003;97:121–7.**

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Melanoma is highly unresponsive to chemotherapy, and patients with advanced metastatic melanoma (MM) have a poor prognosis, with median survivals in the range of 6–9 months. Current treatment options for patients with advanced MM include single-agent and combination chemotherapy, immunotherapy with interleukin-2 (IL-2) and interferon α (IFN-α), and chemoimmunotherapy regimens. Alkylating agents, including dacarbazine (DTIC) and nitrosoureas, and platinum compounds all have demonstrated activity in MM, producing response rates of 10–25%, although responses generally are partial and of short duration (i.e., 3–6 months).[1–5] Widely used combination chemotherapy regimens have improved overall re-

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sponse rates but have not increased the rate of durable complete responses (CRs) or improved survival compared with single-agent DTIC.[6–9] Biologic agents have yielded response rates in the range of 15–20% and durable CRs in a small subset of patients (5–10%).[10–12] Finally, chemoimmunotherapy regimens have produced high objective response rates on the order of 50% but have not yielded a proportional improvement in the rate of durable CRs.[13–19] Ultimately, none of these regimens has improved survival for the majority of patients with advanced MM.

Failure of systemic therapy for MM often is the result of central nervous system (CNS) metastasis, which is associated with an ominous prognosis. The CNS is the site of initial recurrence or progression in approximately 50% of patients with MM who respond to chemoimmunotherapy,[20,21] and the CNS often is the only site of disease progression.[22] Because most of the agents used to treat patients with MM do not effectively penetrate the CNS, the brain is left unprotected. Therefore, agents that have activity against melanoma and can effectively penetrate the CNS are needed.

Temozolomide (TMZ; Temodar®; Schering-Plough, Kenilworth, NJ) is a well-tolerated, oral, nonclassic alkylating agent with excellent CNS penetration that has demonstrated activity against MM.[23–26] In a randomized, multicenter, Phase III trial, 305 patients with advanced MM without CNS metastases were treated with either oral TMZ (200 mg/m^2 per day for 5 days every 28 days) or intravenous DTIC (250 mg/m^2 per day for 5 days every 21 days).[26] In that trial, TMZ was at least as effective as DTIC in terms of response rate, time to disease progression, and overall survival. Furthermore, TMZ was well tolerated, with minor, noncumulative hematologic toxicity. Transient Grade 3–4 myelosuppression occurred in $<$ 10% of patients.[26,27] The randomized comparison of TMZ with DTIC also demonstrated substantial improvements in quality-of-life scores for patients who were treated with TMZ.[26]

Most important is that TMZ may treat and prevent brain metastases more effectively than other agents because of its excellent CNS penetration. TMZ reaches concentrations in the CNS that are approximately 30–40% of the plasma concentration.[28,29] There is also clinical evidence that TMZ may reduce the incidence of CNS recurrence. In a retrospective analysis comparing patients with MM who were treated either with DTIC (n = 21 patients) or with TMZ (n = 19 patients), there were significantly fewer instances of CNS recurrence in the TMZ-treated patients (10% vs. 38%).[22] Moreover, in a recent study of 48 patients with MM who were treated with a combination of cisplatin, vinblastine, TMZ, IL-2, and INF-α (CVT regimen), 42% achieved a partial response (PR), and 12.5% achieved a CR.[21] Among responders to CVT, only 1 patient had an initial CNS recurrence.

The promising activity of TMZ in MM provided the rationale for initiating a pilot study of TMZ in combination with IFN-α2b, another active agent for the treatment of patients with MM. Our primary objectives in the current study were to determine the multidose pharmacokinetics (PK) of TMZ when administered in combination with IFN-α2b and to determine the maximum tolerated dose (MTD) of IFN-α2b in combination with standard doses of TMZ.

MATERIALS AND METHODS

Patients

Patients were considered eligible for the study if they had histologically confirmed, surgically incurable, Stage IV MM (any T, any N, M1–M3); measurable and evaluable disease; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate organ function (serum creatinine within the upper limit of normal [ULN], bilirubin $<$ 1.5 $\times$ ULN, and liver enzymes $<$ 2 $\times$ ULN), adequate hematologic values (absolute neutrophil count $>$ 1500 cells/μL and platelets $>$ 100,000/μL) at baseline; and no prior chemotherapy or biologic therapy for Stage IV disease. Bone metastases were not considered measurable and evaluable disease. Patients with CNS metastasis, as determined by brain imaging studies, were excluded. Patients who had received one prior adjuvant therapy regimen were eligible. All patients provided informed written consent.

Study Design

The study was a single-center, open-label, Phase I study of subcutaneous IFN-α2b in combination with TMZ for the treatment of patients with MM. The protocol was approved by the Institutional Review Board at the University of Pittsburgh. The primary objectives of the study were to examine the plasma PK of TMZ plus IFN-α2b and establish the MTD of IFN-α2b in combination with standard doses of TMZ. All patients received IFN-α2b subcutaneously 3 times per week starting on Day 1 of TMZ treatment. TMZ was administered for 5 days every 28-day cycle. A cohort of 17 patients received TMZ (150 mg/m^2 per day) for 5 days plus escalating doses of IFN-α2b (5.0 million International Units [MIU]/m^2 per day, 7.5 MIU/m^2 per day, or 10.0 MIU/m^2 per day) 3 times per week. A second cohort of 6 patients received TMZ (200 mg/m^2 per day) plus IFN-α2b (5 MIU/m^2 per day) 3 times per week. TMZ doses were rounded to the nearest 20 mg to accommodate capsule strength. Patients were

treated until they experienced disease progression or withdrew from the study for toxicity. Patients received premedication with oral acetaminophen every 4 hours (2600–3000 mg per day) prior to initiating IFN-α2b therapy and continuing until tolerance to fever developed.

Dose-limiting toxicity (DLT) was defined as the occurrence of 1 of the following adverse events within the first 28 days after the administration of TMZ: Common Toxicity Criteria (CTC) Grade 4 neutropenia that did not resolve within 5 days; Grade 4 anemia; Grade 3 or 4 thrombocytopenia; serum creatinine $> 2 \times$ normal levels; Grade 4 emesis that did not resolve with antiemetics; or other CTC Grade 3 events, as defined in the protocol. Adverse events that were not considered DLT included Grade 3 nausea or emesis; Grade 3 fever in the absence of infection; and Grade 3 or 4 flu-like symptoms (including fatigue), neurotoxicity, cardioarrythmia, nausea, emesis, or diarrhea (although these events may have required dose modification). Patients with DLT were permitted to remain on therapy with appropriate dose modifications at the discretion of the investigator. The efficacy end point was the objective response rate (PRs and CRs). Standard response criteria based on measurable disease were used, and responses were confirmed on two consecutive scans at least 4 weeks apart.

Patients initially were treated with a starting dose of TMZ 200 mg/m^2 per day plus IFN-α2b 5 MIU/m^2 per day. However, due to dose-limiting Grade 3 and 4 thrombocytopenia in the first 2 patients, the protocol was amended so that all subsequent patients were to be treated with TMZ 150 mg/m^2 per day plus escalating doses of IFN-α2b. The plan was to enroll six patients at each dose level. The MTD was defined as the dose at which no more than one of six patients experienced DLT and at least two of six patients experienced DLT at the next higher dose level.

PK Analyses

To examine the PK of TMZ, blood samples were obtained prior to the initial dose and at 0.25 hours, 0.50 hours, 0.75 hours, 1.00 hour, 1.50 hours, 2.00 hours, 3.00 hours, 4.00 hours, and 6.00 hours postdose on Day 5 of Cycles 1 and 2. PK analyses of TMZ included maximum plasma concentration (C_{max}), time to maximum plasma concentration, area under the curve as a function of time (AUC[tf]), terminal elimination half-life ($t_{1/2}$), and total body clearance.

RESULTS

Patients

Patient demographics, disease history, and performance status are summarized in Table 1. Twenty-three patients were enrolled (16 males and 7 females), with a median age of 41 years (range, 24–80 years). All patients had an ECOG performance status of 0 or 1. Fifteen patients had regional disease at initial diagnosis: Four patients had Stage IB disease (T1b–T2a, N0, M0), 3 patients had Stage IIA disease (T2b–T3a, N0, M0), 4 patients had Stage IIB disease (T3b–T4a, N0, M0), and 4 patients had Stage III disease (T1–T4b, N1a–N2c, and M0 or any T, N3, M0). Only four of these patients had received prior adjuvant IFN-α2b therapy. The remaining eight patients were newly diagnosed with Stage IV disease (any T, any N, M1–M3). Patients received a median of 2 cycles of therapy (range, 1–11 cycles).

TABLE 1
Patient Demographics (N = 23 patients)

Parameter	No. of patients (%)
Age (yrs)	
Median	41
Range	24–80
Gender	
Male	16 (70)
Female	7 (30)
ECOG performance status	
0	13 (57)
1	10 (43)
Stage IV disease at initial diagnosis	8 (35)
Prior adjuvant therapy	
No	19 (83)
Yes	4 (17)
Type of prior therapy	
Biologic	5 (22)
Radiotherapy	5 (22)

ECOG: Eastern Cooperative Oncology Group.

MTD

Dose-limiting Grade 3 and 4 thrombocytopenia occurred in two of three patients in the initial cohort of patients who were treated with TMZ 200 mg/m^2 per day plus IFN-α2b 5 MIU/m^2 per day. However, because one of the patients in this initial cohort was elderly and had considerable comorbidity, an additional group of three patients was treated at this dose level. In this second cohort, no DLT occurred; thus, it was determined that TMZ 200 mg/m^2 plus IFN-α2b 5 MIU/m^2 was a safe dose. However, the initial toxicity observed at this dose level prompted a protocol amendment to reduce the dose of TMZ to 150 mg/m^2 per day in all subsequent patients, and the effect of IFN-α2b dose escalation with the 200 mg/m^2 dose of TMZ was not examined.

Seventeen patients received TMZ 150 mg/m^2 per

day and escalating doses of IFN-α2b. Of these 17 patients, 4 patients received IFN-α2b 5.0 MIU/m^2 per day (Group A), 7 patients received IFN-α2b 7.5 MIU/m^2 per day (Group B), and 6 patients received IFN-α2b 10.0 MIU/m^2 per day (Group C). Only one of seven patients in Group B and one of six patients in Group C had DLT (Grade 3 or 4 thrombocytopenia). However, two patients in Group C experienced serious adverse events requiring hospitalization and were discontinued from the study for adverse events. One patient had severe anorexia, dehydration, nausea, emesis, and sepsis. The second patient had Grade 3 elevation of liver enzymes (although this patient had a prior history of exposure to hazardous chemicals). Thus, it was determined that the MTD for the combined regimen was TMZ 150 mg/m^2 per day plus IFN-α2b 7.5 MIU/m^2 per day, 3 times per week. Therefore, currently, the MTD for the combination of TMZ and IFN-α2b is considered either TMZ 150 mg/m^2 per day plus IFN-α2b 7.5 MIU/m^2 per day, 3 times per week, or TMZ 200 mg/m^2 per day plus IFN-α2b 5.0 MIU/m^2 per day, 3 times per week.

Safety Profile

Treatment-related adverse events in the group of patients who received either TMZ 150 mg/m^2 per day plus IFN-α2b 5–10 MIU/m^2 3 times per week or TMZ 200 mg/m^2 per day TMZ plus 5 MIU/m^2 IFN-α2b 3 times per week are detailed in Table 2. The most common adverse events were fatigue, fever, emesis, and anxiety. At the higher dose of IFN-α2b, several patients had Grade 3 fatigue, and one patient had Grade 4 fatigue. Generally, fatigue was manageable and reversible. Mild-to-moderate fever, nausea, emesis, and diarrhea occurred in a large portion of patients but responded to palliative care. Injection-site reactions were common but not severe. Although depression was common, it was not severe. Both anxiety and insomnia were common and appeared to be dose dependent; however, the majority of incidents were mild to moderate in severity. Grade 1–2 hypotension, which occurred in approximately one-third of patients, was controlled easily, and blood pressure returned to normal on treatment cessation. Hepatic toxicity was rare, although elevated liver enzymes resulted in study discontinuation in one patient who was treated at the highest dose of IFN-α2b. Six patients had decreased white blood cell counts (Grade 1–2 leukopenia [n = 5 patients] and Grade 3 neutropenia [n = 1 patient]), but these events were mostly mild to moderate in severity, manageable, and reversible. The most common hematologic DLT was thrombocytopenia, as described above. In addition, one patient developed Grade 3 sepsis.

TABLE 2
Treatment-Emergent Adverse Events by Severity in Each Temozolomide Dose Group

	No. of patients (%)			
	150 mg/m^2 (n = 17 patients)		200 mg/m^2 (n = 6 patients)	
Adverse event	All grades	Grade 3/4	All grades	Grade 3/4
Fatigue	17 (100)	5 (29)	5 (83)	1 (17)
Fever	15 (88)	0	5 (83)	0
Nausea	15 (88)	3 (18)	5 (83)	0
Emesis	13 (76)	3 (18)	5 (83)	0
Anxiety	10 (59)	1 (6)	0	0
Diarrhea	8 (47)	1 (6)	3 (50)	0
Injection site reaction	7 (41)	0	0	0
Depression	6 (35)	0	1 (17)	0
Hypotension	5 (29)	0	1 (17)	0
Leukopenia	1 (6)	0	1 (17)	1 (17)
Insomnia	4 (24)	0	2 (33)	0
Elevated AST	1 (6)	1 (6)	0	0
Elevated ALT	2 (12)	1 (6)	1 (17)	0
Neutropenia	1 (6)	0	1 (17)	1 (17)
Thrombocytopenia	2 (12)	2 (12)	2 (33)	2 (33)
Sepsis	1 (6)	1 (6)	1 (17)	0

AST: aspartate aminotransferase; ALT: alanine aminotransferase.

TABLE 3
Best Tumor Response by Temozolomide Dose

	No. of patients (%)	
Best response	TMZ 150 mg and IFN-α2b 5–10 MIU/m^2/day (n = 17 patients)	TMZ 200 mg and IFN-α2b 5 MIU/m^2/day (n = 6 patients)
Complete response	1 (6)	0
Partial response	1 (6)	2 (33)
Stable disease	4 (24)	0
Progressive disease	11 (65)	4 (66)

TMZ: temozolomide; IFN-α2b: interferon α-2b; MIU: million International Units.

Efficacy

The best tumor responses for both treatment regimens are presented in Table 3. Overall, 4 of 23 patients (17%) had an objective response (95% confidence interval, 0.017–0.324), including 1 CR and 3 PRs. Among 17 patients who were treated with TMZ 150 mg/m^2, 1 patient with multiple cutaneous lesions achieved a CR after 10 cycles, and 1 patient achieved a PR in multiple lymph node and subcutaneous satellite lesions after 2 cycles. In addition, four patients had stable disease for 4 months, 5 months, 6 months, and $\geq$ 7 months. Among 6 patients who were treated with TMZ 200 mg/m^2 plus IFN-α2b 5 MIU/m^2, 2 patients achieved a PR: One patient had a PR after 2 cycles in multiple

TABLE 4
Pharmacokinetics of Temozolomide[a]

Parameter	Temozolomide dose	
	150 mg/m^2 (n = 15 patients)	200 mg/m^2 (n = 6 patients)
C_{max} (μg/mL)	7.18	10.50
T_{max} hours	1.30	0.90
$AUC_{0-\infty}$, (μg·hour/mL)	23.30	30.20
$T_{1/2}$ (hours)	1.87	1.90
Clearance (mL/kg/minute)	2.57	2.62
Volume of distribution (L/kg)	0.42	0.42

C_{max}: maximum observed plasma concentration; T_{max}: time of maximum observed plasma concentration; $AUC_{0-\infty}$: area under the plasma concentration-time curve from Time 0 to the final quantifiable sample; $t_{1/2}$: terminal phase half-life.

[a] Pharmacokinetic parameters were determined after 5 days of oral temozolomide in combination with interferon α-2b on Day 1.

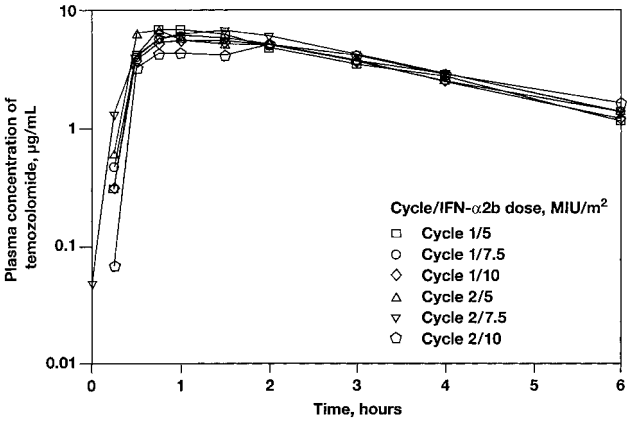

FIGURE 1. Mean plasma concentration of temozolomide after daily oral administration of 150 mg/m^2 per day in combination with various doses of interferon α-2b (IFN-α2b). MIU: million International Units.

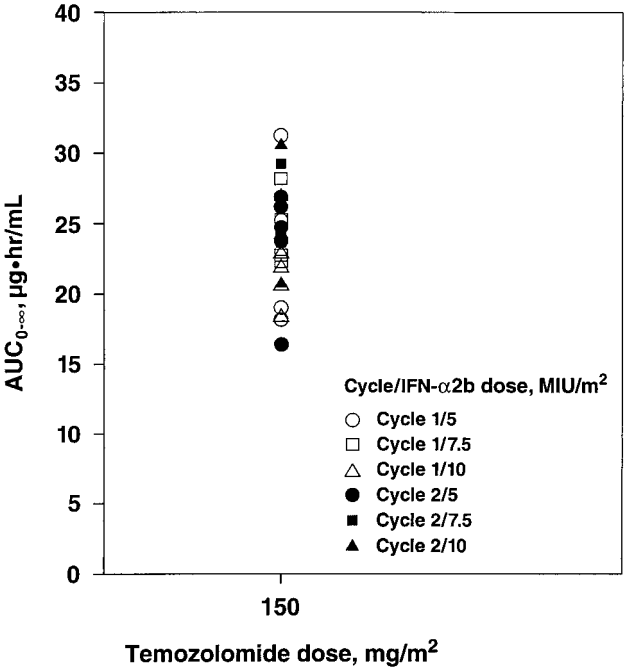

FIGURE 2. Area under the concentration curve from time zero to infinity ($AUC_{0-\infty}$) for temozolomide on Day 5 after daily oral administration of 150 mg/m^2 per day in combination with various doses of interferon α-2b (IFN-α2b). MIU: million International Units.

lung and liver metastases that lasted 10 months, and the second patient had a PR in cervical lymph nodes after 5 cycles but then progressed rapidly. The median survival was 9 months for all 23 patients (range, 1–35 months), and 4 patients remained alive at last follow-up at ≥ 7 months to ≥ 12 months from the start of treatment.

PK Analysis

The PK data for both treatment regimens are summarized in Table 4. Twenty-one patients were evaluable (15 patients in the TMZ 150 mg/m^2 group and 6 patients in the TMZ 200 mg/m^2 group). TMZ was absorbed and eliminated rapidly with no significant plasma accumulation. The observed C_{max} for TMZ at 150 mg/m^2 was 7.18 μg/mL, and the observed C_{max} for TMZ at 200 mg/m^2 was 10.50 μg/mL. The $AUC_{0-\infty}$, which expresses drug concentration over time, increased in a dose dependent manner. The $AUC_{0-\infty}$ for TMZ at 150 mg/m^2 was 23.3 μg per hour per mL, and the AUC(tf) for TMZ at 200 mg/m^2 was 30.20 μg per hour per mL. The $t_{1/2}$ was 1.87 hours for TMZ at 150 mg/m^2 and 1.90 hours for TMZ at 200 mg/m^2. TMZ clearance was 2.57 mL/kg per minute for the lower dose and 2.62 mL/kg per minute for the higher dose. Coadministration of IFN-α2b with TMZ had no apparent effect on the PK of TMZ. Within the group that received TMZ 150 mg/m^2 per day, the plasma concentration (Fig. 1) and the $AUC_{0-\infty}$ (Fig. 2) for TMZ were similar regardless of the coadministered dose of IFN-α2b.

DISCUSSION

The results of the current study indicate that TMZ can be combined safely with IFN-α2b. Fatigue, fever, and emesis were the most common side effects of this regimen but were manageable and reversible. Leukopenia and abnormalities in hepatic enzymes were less common and also were manageable and reversible. Thrombocytopenia was the primary DLT. The combination showed promising activity against MM, with a 17% overall response rate. These results suggest that TMZ can be combined safely with IFN-α2b. Therefore, chemoimmunotherapy regimens containing TMZ

should be investigated further for the treatment of patients with MM.

The safety profile for the combination of TMZ and IFN-α2b was similar to that reported for each agent separately and included manageable fatigue, nausea, emesis, and myelosuppression.[26] Patients who received the MTD experienced predominantly mild-to-moderate toxicity, mainly fatigue, fever, emesis, and myelosuppression. Although thrombocytopenia was dose limiting in 2 of the first 3 patients who were treated with TMZ 200 mg/m^2 per day plus IFN-α2b 5 MIU/m^2 per day, 3 additional patients tolerated this dose without thrombocytopenia, and only 2 of 17 patients who were treated with TMZ 150 mg/m^2 per day experienced thrombocytopenia at any of the IFN-α2b doses tested. Moreover, no cumulative toxicities were observed with this regimen.

The PK profile of TMZ observed in this study was consistent with previously reported studies,[23,27,30–34] and coadministration of IFN-α2b did not affect the plasma concentration or AUC of TMZ across the tested dose range, suggesting that there were no PK interactions between TMZ and IFN-α2b. TMZ was absorbed and eliminated rapidly, and the maximum concentration was reached after 1.3 hours for the TMZ 150 mg/m^2 dose and 0.9 hours for the TMZ 200 mg/m^2 dose. Other studies have shown similar times to C_{max}. The $t_{1/2}$ (approximately 1.9 hours for both TMZ doses) also was similar to that demonstrated in prior studies. TMZ demonstrated linear PK with increasing dose. Therefore, as expected, because TMZ is not metabolized in the liver, IFN-α2b did not affect adversely the PK of TMZ.

Because both TMZ and IFN-α2b are active agents in the treatment of patients with MM, the goal of this study was to develop a regimen combining these two agents and to investigate the potential effects of IFN-α2b on the PK of TMZ. Moreover, because TMZ penetrates the CNS, it may play a role in the treatment of patients who are at high risk of developing CNS recurrences. Brain metastases are a significant clinical problem in patients with advanced MM. The CNS is a frequent site of initial recurrence or disease progression in patients who are treated with chemoimmunotherapy,[20,21] and 55–75% of patients with MM have brain metastases at autopsy.[35] Therefore, a regimen with activity against melanoma in the CNS would be an important advance. Unfortunately, no conclusions can be drawn from this study regarding the activity of TMZ in brain metastases, because patients did not receive computed tomography scans or magnetic resonance imaging studies as routine follow-up at the time of disease progression. Only one patient had disease that progressed clinically in the brain.

Several studies suggest that TMZ, either alone or in combination with other agents, has activity against melanoma in the CNS. Notably, Bafaloukos et al.[36] recently demonstrated that the combination of TMZ plus docetaxel produced PRs in three patients with brain metastases from MM. A retrospective study reported by Summers et al.[22] suggested that TMZ may reduce the incidence of CNS metastases compared with DTIC. Furthermore, in a Phase II pilot study of a chemoimmunotherapy regimen in which DTIC was replaced by TMZ in combination with cisplatin, vinblastine, IL-2, and IFN-α2b, tumor responses were seen in 20 of 48 patients (42%), and only 1 patient had an initial CNS recurrence.[21] Therefore, it is reasonable based on these data to investigate further the activity of TMZ in combination with biologic agents for the treatment of patients with MM.

The current study suggests that the combination of TMZ and IFN-α2b is active and warrants further investigation in larger Phase II trials. The combination of TMZ and IFN-α2b was tolerated well compared with other widely used chemoimmunotherapy regimens, and IFN-α2b did not affect the PK of TMZ. Because TMZ is well tolerated and has antitumor activity that is comparable with DTIC and activity against brain metastases, TMZ has potential as a replacement for DTIC in further investigations of chemoimmunotherapy regimens for patients with MM. Randomized clinical trials will be necessary to determine whether TMZ combined with immunotherapy will reduce morbidity and mortality due to brain metastases and will improve survival compared with other widely used regimens for patients with MM.

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