INTRODUCTION

Each year, about 200,000 cases of melanoma are diagnosed and there are 48,000 melanoma-related deaths worldwide. The incidence of metastatic melanoma increases every year, and the death rate continues to rise faster than that of most cancers. Melanoma is surgically curable when discovered at an early stage; however, once regional and systemic spread occurs, treatment options are limited and generally considered ineffective. The prognosis for metastatic melanoma is poorer and the 5-year survival rate is less than 10%. In recent years, with the development of targeted immune therapy and individualized targeted therapy, the treatment of melanoma made significant progress. They include kinase inhibitors acting on cellular pathways, anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody, PD-1 monoclonal antibody and so on. But these new medicines are very expensive. Therefore, chemotherapy for melanoma patients is still an important means of treatment at this stage. Adjuvant therapy is partially effective, and a number of chemotherapeutic agents have activity in metastatic melanoma, including dacarbazine (DTIC), temozolomide (TMZ), the nitrosoureas, platinum analogs, vinca alkaloids, and the taxanes.

TMZ is an oral agent, therefore, it has potential advantages over DTIC in terms of convenience. It can cross the blood-brain barrier (BBB), which could potentially reduce the incidence of brain metastases. However, the response rate of TMZ is generally low due to drug resistance. Several studies have focused on the effectiveness of TMZ in malignant melanoma. In this review, we provide an overview of recent advances of TMZ for this disease.

Comparison of TMZ and DTIC for treating malignant melanoma:

DTIC, a cell cycle-nonspecific antineoplastic agent, is the most tested single chemotherapeutic agent. Hepatic metabolism is required to yield the active metabolite 5-(3-methyl-1-triazeno) imidazole-4-carboxamide (MTIC) of DTIC. MTIC decomposes into a purine and a methyldiazonium ion, which is the active alkylating species. The usefulness of DTIC may, therefore, be limited in patients with liver metastases. Furthermore, DTIC does not cross the BBB, and is therefore ineffective for treating brain metastases. While the prognosis is currently unpromising, chemotherapy plays a palliative role for patients with metastatic melanoma. The toxicity of treatment regimens based on DTIC and TMZ do not differ significantly, although TMZ is costlier. These findings provide a reference for future researchers via a comprehensive analysis of the relevant literature.


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Efficacy and safety of TMZ versus DTIC: In a phase III trial involving 305 patients, TMZ was not significantly more efficacious than DTIC in terms of overall survival (OS, 7.7 vs. 6.4 months) and progression-free survival (PFS, 1.9 vs. 1.5 months).7 Patel et al. later conducted a large, randomized, open-label phase III study to determine whether an extended schedule of TMZ would be more effective than standard single-agent DTIC for treating patients with metastatic melanoma.15 They found no difference in either OS (9.1 vs. 9.4 months) or PFS (2.3 vs. 2.2 months).15 Recently, Teimouri et al. compared the effectiveness and side effects of TMZ with that of DTIC via a meta-analysis involving 1314 patients. They found a non-significant relative risk (RR) of 0.83 [95% confidence interval (CI): 0.26 - 2.64, p = 0.76] for complete response, 1.05 (95% CI: 0.85 - 1.3, p = 0.65) for stable disease, and 2.64 (95% CI: 0.97 - 1.36, p = 0.11) for disease control rate.16 Compared to that of DTIC, the RR for TMZ non-hematological and hematological side effects, such as anemia, neutropenia, and thrombocytopenia, was non-significant in all cases, but the RR for TMZ lymphopenia was 3.79 (95% CI: 1.38 - 10.39, p = 0.01), which was significant. That is to say, the authors found no significant difference in the efficacy and side effects of the two agents, except that TMZ increased the prevalence of lymphopenia.

Health-related quality of life and cost-effectiveness analysis of TMZ versus DTIC: Given the poor prognosis and lack of curative treatments, the primary aim of therapy for metastatic melanoma is palliation, maximizing symptom control while minimizing toxicity. In such patients, for whom a cure is currently unavailable, stable or improved health-related quality of life (HRQL) is essential to avoid sacrificing quality of life. Following a randomized controlled trial, Middleton and colleagues reported that patients treated with TMZ had better physical function and less fatigue and sleep disturbances than DTIC-treated patients after 12 weeks of chemotherapy.7 Using a clinical trial that compared TMZ and DTIC in patients with metastatic melanoma, Kiebert et al. provided further insight into HRQL. The study suggested that treatment with TMZ led to important functional improvements and decreased symptoms compared to DTIC treatment.17 In addition, financial difficulties also must be addressed, which spurred Hillner et al. to perform an economic analysis of TMZ versus DTIC:

- **Efficacy and safety of TMZ versus DTIC:**
  - TMZ was not significantly more efficacious than DTIC in terms of overall survival (OS, 7.7 vs. 6.4 months) and progression-free survival (PFS, 1.9 vs. 1.5 months).7
  - Patel et al. reported a non-significant relative risk (RR) of 0.83 [95% confidence interval (CI): 0.26 - 2.64, p = 0.76] for complete response.
  - The RR for TMZ non-hematological and hematological side effects, such as anemia, neutropenia, and thrombocytopenia, was non-significant in all cases, but the RR for TMZ lymphopenia was 3.79 (95% CI: 1.38 - 10.39, p = 0.01), which was significant.

- **Health-related quality of life and cost-effectiveness analysis of TMZ versus DTIC:**
  - Middleton and colleagues reported that patients treated with TMZ had better physical function and less fatigue and sleep disturbances than DTIC-treated patients after 12 weeks of chemotherapy.
  - Kiebert et al. provided further insight into HRQL. The study suggested that treatment with TMZ led to important functional improvements and decreased symptoms compared to DTIC treatment.

### Table I: TMZ in treatment of melanoma brain metastases.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Treatment</th>
<th>N</th>
<th>ORR (%)</th>
<th>Median PFS/TTP</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins, et al. (2002)21</td>
<td>TMZ, CDDP, vinblastine, IL-2, IFN-α2b</td>
<td>48</td>
<td>47</td>
<td>3 m</td>
<td>7.5 m</td>
</tr>
<tr>
<td>Riddell, et al. (2004)22</td>
<td>TMZ and IFN-α</td>
<td>40</td>
<td>12.5</td>
<td>2.6 m</td>
<td>11.8 m</td>
</tr>
<tr>
<td>Ready, et al. (2005)23</td>
<td>TMZ, CDDP, IL-2, IFN-α2b</td>
<td>21</td>
<td>24</td>
<td>unknown</td>
<td>9.7 m</td>
</tr>
<tr>
<td>Weber, et al. (2005)24</td>
<td>TMZ, GM-CSF, IL-2, IFN-α2b</td>
<td>31</td>
<td>26</td>
<td>4.9 m</td>
<td>13.1 m</td>
</tr>
<tr>
<td>Ron, et al. (2006)25</td>
<td>TMZ, CDDP, vinblastine, IL-2, IFN-α</td>
<td>23</td>
<td>43.4</td>
<td>unknown</td>
<td>18.6 m</td>
</tr>
</tbody>
</table>

N: Number of patients; m: Month; ORR: OR rate; GM-CSF: Granulocyte-macrophage colony-stimulating factor.
By contrast, in brain magnetic resonance imaging carried out at 3-month intervals, Gonzalez et al. reported similar CNS failure rates in TMZ schedules compared to the DTIC regimen.26 A phase II study that used cisplatin (CDDP) and TMZ reported a high percentage of CNS recurrences (10 of 28 patients).27 However, these studies were either phase II or retrospective; Chiarion-Sileni et al. conducted a randomized, multi-center phase III study to compare the incidence of CNS metastases between a TMZ-based regimen (CTI) and a DTIC-based regimen (CDI) in untreated stage IV melanoma patients.28 This was the first prospective study to examine whether TMZ decreases the incidence of CNS metastases and alters its clinical course in melanoma patients. The 1-year cumulative CNS incidence failure was 20.6% for CTI and 31.1% for CDI (p = 0.22). The median survival time for the CTI and CDI arm was 8.4 months and 8.7 months, respectively; in patients with CNS metastases, the median survival time for the CTI and CDI arm was 13.5 months and 11.5 months, respectively. No difference in toxicity was observed between the two treatment arms, suggesting that TMZ significantly influenced neither the incidence of CNS recurrence nor the clinical course of CNS involvement.

TMZ may be efficacious in association with whole-brain radiation therapy, and some studies have shown that TMZ combined with radiotherapy may prolong survival compared to TMZ alone without radiotherapy.29 However, many clinical trials have shown that TMZ alone or in association with other therapeutic agents or with concomitant radiotherapy has only modest efficacy against brain metastases. Thus, the role of TMZ in treating brain metastasis remains unclear.30 Owing to these non-definitive results, there has been no consensus regarding the efficacy of TMZ in brain metastasis. More large-scale, randomized, controlled prospective studies are required to confirm whether TMZ prevents brain metastases, improves the response rate, and prolongs the survival of patients with malignant melanoma and brain metastases.

**Mechanisms of TMZ multidrug resistance:** During the initial phase of chemotherapy, an anti-cancer drug might not kill all of the cancer cells. Some cells survive the treatment and initiate further regrowth of cancer cells. In many cases, the new cells become resistant to treatment. To overcome resistance to the previously used drug, treatment with another agent or a combination of several agents with different mechanisms of action is administered. However, in the late phase of chemotherapy, cancer cells become resistant not only to the drugs previously used for treatment but also to many anti-cancer agents with distinct mechanisms of cancer killing.31 The therapeutic benefit of temozolomide depends on its ability to alkylate and/or methylate DNA, which most often occurs at the N-7 or O-6 positions of guanine residues. This methylation damages the DNA and triggers the death of tumor cells. However, some tumor cells are able to repair this type of DNA damage, and therefore diminish the therapeutic efficacy of temozolomide, by expressing a protein O6-alkylguanine DNA alkyltransferase (AGT) encoded in humans by the O-6-methylguanine-DNA methyltransferase (MGMT) gene.32 As prodrugs of the cytotoxic agent MTIC, TMZ acts through the same mechanism as DTIC. MTIC methylates the O6-guanine of DNA, generating cytotoxic adducts that result in the initiation of cellular repair mechanisms or apoptosis.15,33 O-6-methylguanine (O6meG) is the most cytotoxic of all methyl-DNA lesions caused by TMZ or DTIC. However, the response rate of both TMZ and DTIC is generally low and few patients attain complete remission. This is partly due to drug resistance; although there are many mechanisms of resistance. A key mechanism of resistance is O6meG-DNA methyltransferase (MGMT) overexpression. MGMT repairs the TMZ-induced DNA lesion O6meG by removing the methyl group from guanine to a cysteine residue.34 If MGMT repair fails, O6 meG mismatches with thymine, subsequently activating the mismatch repair system (MMR).35 The MMR excises the mispaired base to reinsert cytosine or thymine again opposite to O6meG, and the repeated futile cycles of MMR intervention eventually cause DNA strand breaks, growth arrest, or apoptosis.36,37 Either low or high host expression of MGMT, MLH1, and MSH2 may serve as a marker for reduced hemato logic side effects of TMZ or DTIC, but not for treatment efficacy in melanoma. The genetic variant rs2303428 (MSH2) might serve as a predictive marker for hematologic side effects and treatment response.33 **Increasing TMZ effectiveness in malignant tumor:** The simplest way to overcome drug resistance is to increase the drug concentration. However, high doses of chemotherapeutic agents are extremely dangerous. When a drug is not targeted specifically to cancer cells, it can potentially induce severe adverse side effects in healthy tissues and cells. Therefore, this approach cannot be considered viable for overcoming multidrug resistance. Different approaches have been developed to overcome these delinquencies of the systemic delivery of high-dose anti-cancer drugs, including the combined use of multiple drugs with different mechanisms of action and targeting anti-cancer agents to tumors.33 **Combining TMZ with other anti-tumor agents:** In vitro studies have demonstrated that CDDP downregulates MGMT activity, suggesting that CDDP enhances the anti-tumor activity of TMZ. Bafaloukos et al. conducted a randomized phase II study to evaluate and compare the activity and safety profile of combination versus single-agent TMZ in patients with advanced melanoma.38
However, they observed no clear benefit in terms of response rates, median time to progression (TTP), or OS following TMZ + CDDP treatment. Additionally, the combination was associated with higher incidence of grade 3 and 4 emesis. A phase I dose expansion and phase II study of TMZ in combination with the MGMT inhibitor lomeguatrib examined this further, reporting similar anti-tumor activity in the two treatment arms and no reversal of TMZ resistance with the addition of lomeguatrib. Nonetheless, several studies on animal models have demonstrated that decreasing MGMT levels with the gene therapy agent could overcome TMZ resistance and enhance tumor cell death. Another study showed that a replication-defective adenovirus expressing interleukin-24 (IL-24) sensitized TMZ-resistant melanoma cells by inhibiting MGMT expression. The authors’ previous laboratory-based study demonstrated that a KI67 promoter-controlled ZD55-II-24 could improve the antitumor effects of the alkylating agent TMZ in melanoma cells. Followed, we found that treatment of melanoma with KI67-ZD55-II-24 plus TMZ in vivo significantly reduces tumor growth and increases apoptosis with inhibition of the expression of MGMT. Kato et al. showed that transducing TMZ-resistant glioma cells with a LipoTrust liposome containing MGMT small interfering RNA enhanced their sensitivity to TMZ. The above-indicated MGMT inactivation by gene therapy may be an approach for overcoming TMZ resistance in melanoma. However, Christina showed that there was no difference in terms of PFS (p=0.972) or OS (p=0.126) in patients who received DTIC alone (n=20) compared with those who received DTIC in combination (n=21). Many cancers, particularly melanomas, are resistant to apoptosis due to upregulation of anti-apoptotic Bcl-2 family members. The BH3 mimetic ABT-737, which induces apoptosis by targeting pro-survival Bcl-2 family members, enhances the efficacy of many conventional chemotherapeutic agents in multiple cancers. Reuland et al. found that combining TMZ and ABT-737 induced strong synergistic apoptosis in multiple human melanoma cell lines and drastically reduced tumor growth in a mouse xenograft model. These results demonstrate that targeting anti-apoptotic Bcl-2 family members is a promising method for enhancing TMZ efficacy for treating metastatic melanoma.

### Table II: TMZ-based combination therapy in melanoma metastases treatment.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Treatment</th>
<th>N</th>
<th>ORR (%)</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danson, et al. (2003)</td>
<td>TMZ/Thalidomide</td>
<td>60</td>
<td>15</td>
<td>Median OS is 7.3 months</td>
</tr>
<tr>
<td>Yoon, et al. (2010)</td>
<td>TMZ/Docetaxel</td>
<td>38</td>
<td>13</td>
<td>The median time to disease progression was 8 weeks, and the overall survival duration was 26 weeks</td>
</tr>
<tr>
<td>Clark, et al. (2010)</td>
<td>TMZ/Thalidomide</td>
<td>62</td>
<td>13</td>
<td>Median PFS was 2 months, median OS was 8 months, and the estimated 1-year overall survival was 35%</td>
</tr>
<tr>
<td>Su, et al. (2010)</td>
<td>TMZ/Bortezomib</td>
<td>19</td>
<td>Unknown</td>
<td>Median PFS is 2.1 months and OS were 6.3 months</td>
</tr>
<tr>
<td>Von Moos, et al. (2012)</td>
<td>TMZ/Bevacizumab</td>
<td>62</td>
<td>16.1</td>
<td>Median PFS and OS were 4.2 and 9.6 months</td>
</tr>
<tr>
<td>Ott, et al. (2013)</td>
<td>TMZ/Oblimersen</td>
<td>32</td>
<td>40.6</td>
<td>Median PFS was 161 days, the median OS was 336.5 days, and 1-year OS was 50%</td>
</tr>
</tbody>
</table>

N: Number of patients; ORR: OR rate.

### Table III: TMZ and IFN α-2b in metastatic melanoma.

<table>
<thead>
<tr>
<th>Author</th>
<th>TMZ dose</th>
<th>IFN α-2b dose</th>
<th>OR</th>
<th>OS</th>
<th>PFS</th>
<th>Myelotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danson, et al.</td>
<td>200 mg/m² (1)</td>
<td>5 MU TIW</td>
<td>18%</td>
<td>7.7 months</td>
<td>ND (A) Grade III/IV 21%</td>
<td></td>
</tr>
<tr>
<td>Agarwala, et al.</td>
<td>150 mg/m² (1)</td>
<td>5-10 MU/m² TIW</td>
<td>12%</td>
<td>9 months</td>
<td>ND (A) Grade III/IV 0%</td>
<td></td>
</tr>
<tr>
<td>Richtig, et al.</td>
<td>200 mg/m² (1)</td>
<td>5 MU/m² TIW</td>
<td>33%</td>
<td>ND</td>
<td>ND (A) Grade III/IV 17%</td>
<td></td>
</tr>
<tr>
<td>Ridolfi, et al.</td>
<td>200 mg/m² (1)</td>
<td>5 MU TIW</td>
<td>12.5%</td>
<td>11.8 months</td>
<td>2.6 months (A) Grade III/IV 10%</td>
<td></td>
</tr>
<tr>
<td>Kaufmann, et al.</td>
<td>200 mg/m²</td>
<td>5 MU/m² TIW</td>
<td>24.1%</td>
<td>9.7</td>
<td>3.3 months (A) Grade III/IV 20.5%</td>
<td></td>
</tr>
<tr>
<td>Garcia, et al.</td>
<td>150 mg/m² (1)</td>
<td>10 MU b.i.d Pegylated IFN</td>
<td>18.5%</td>
<td>9.5</td>
<td>1.87 months (A) Grade III/IV 18.5%</td>
<td></td>
</tr>
<tr>
<td>Hwu, et al.</td>
<td>75 mg/m²/day (2)</td>
<td>Peg-IFN α-2b 0.5 lg/kg/week</td>
<td>31%</td>
<td>ND</td>
<td>ND (A) Grade III 40%</td>
<td></td>
</tr>
<tr>
<td>Spith, et al.</td>
<td>200 mg/m² (1)</td>
<td>Peg-IFN α-2b 100 lg/week</td>
<td>18.1%</td>
<td>9.4</td>
<td>2.74 months (A) Grade III/IV 23.3%</td>
<td></td>
</tr>
</tbody>
</table>

*Every other day. TMZ = Temozolomide; IFN α = Interferon alpha; n = Number of patients; OR = Overall response; OS = Overall survival; PFS = Progression-free survival; WHO = World Health Organization; MIU = Million IU; TIW = Thrice weekly; ND = No data; BIW = Twice weekly; Peg-IFN α-2b = Pegylated Interferon alpha-2b. (1) Refers to days 1-5 every 28 days; (2) Refers to 6 weeks on/2 weeks off; (A) refers to Leukopenia; (B) refers to Thrombocytopenia.
Quercetin is an effective Hsp27 inhibitor and has been reported to facilitate tumor cell apoptosis, which is a widely distributed bioflavonoid and is known to have antitumor effects. Sang et al. reported Quercetin could enhance TMZ to induced cell growth inhibition when combined with quercetin. TMZ or quercetin anole did not affect caspase-3 activity and cell apoptosis, while TMZ combined with quercetin significantly increased caspase-3 activity and induced cell apoptosis. It was reported that quercetin acts in synergy with TMZ and that when both agents were used in combination, rather than in separate pharmacological application, they induced programmed cell death more effectively.

Chemotherapy and cytokines have different and perhaps synergistic mechanisms of action, therefore, their combination may improve Objective Response (OR) and OS. A randomized, phase III multi-center study by the Dermatologic Cooperative Oncology Group showed that combining TMZ and IFN-β in metastatic melanoma treatment led to a significantly superior OR rate compared to treatment with TMZ alone, but this did not translate into prolonged survival. In neuroblastoma, however, delivering interferon-β (IFN-β) with an adeno-associated virus resulted in synergistic action between TMZ and IFN-β by modulating MGMT expression. Also in combination with TMZ, the applied doses of nonpegylated and peg-IFN display comparable toxic effects (Table III).

In addition, the investigators explored several other drugs to increase the efficacy of TMZ against malignant melanoma. Table III summarizes the results of the relevant clinical studies. The table shows that the use of TMZ combining with other drugs could not improve therapy except of TMZ + Oblimersen treatment. However, we made a meta-analysis in 2013, which showed that the TMZ-combination therapy could moderately improve the response rate without corresponding increased toxicity. But there were some limitations, so future large-scale, high-quality, placebo controlled, double-blind trials are needed.

**Targeted delivery of TMZ to tumor cells by multifunctional nanocarriers:** A recent trend in the pharmaceutical industry is the focus on improving the properties of drugs currently used in various treatments, rather than on creating new drugs. TMZ has poor solubility and stability in water, which results in great difficulty when preparing TMZ injections. Although TMZ is soluble and stable under acidic conditions following oral administration, its half-life is only 1.8 hours and it is rapidly cleared from the circulation. Moreover, TMZ degrades to MTIC in the bloodstream, which is ineffective for treating brain metastases, as MTIC does not cross the BBB. Therefore, the survival rates of patients with metastatic melanoma remain poor. Nanocarriers increase the water solubility of TMZ, subsequently improving its properties. Nanocarriers also cause a sustained release and thus improve the half-life of TMZ under physiological conditions, which protects it from degradation and loss of therapeutic effect. In addition, nanocarriers can cross the BBB, prolonging the half-life of TMZ under physiological conditions, which would also promote greater accumulation of TMZ in the brain metastases site prior to degradation. Patil et al. found that compared with the 1.8 hours half-life of free TMZ, that of TMZ conjugated with a polymer was 5 - 7 hours, and the TMZ nanoconjugate was delivered to brain tumor cells, overcoming drug resistance in the treatment of brain cancer. Huang et al. prepared TMZ solid lipid nanoparticles (TMZ-SLN)s and showed that the TMZ-SLNs exhibited sustained release in vitro release tests. They also found that the TMZ-SLNs can effectively target the brain by crossing the blood-brain barrier. Jain et al. found that TMZ loaded into PLGA nanoparticle had a sustained release of the drug and showed a higher cellular uptake.

Orally administered TMZ is not only delivered to the tumor site, but is also distributed throughout the body indiscriminately. TMZ is toxic, and severe side effects limit the therapeutic dosages. Targeted delivery of TMZ to tumor cells would be highly important for avoiding systemic side effects. In fact, tumor cells can increase the medicine efflux pumps on their membranes, which decreases intracellular concentrations of the drug. Nanomedicine increases the intracellular levels of a medicine by encapsulating it in different nanocarriers that will bypass the efflux pumps. Known as passive targeting, many nanocarriers rely on the so-called enhanced permeability and retention effect to improve tumor localization of the therapeutic agents. In addition, targeting efficiency is substantially enhanced by combining nanoparticles with specific antibodies or their fragments, peptides, lectins, sugars, and many other targeting moieties. Ding et al. demonstrated that DTIC-PLA-DR5 mAb nanoparticles (DTIC-NPs-DR5 mAb) are an active targeting medicine delivery system which can specifically target DR5-overexpressing malignant melanoma cells and become efficiently internalized in vitro experiments. Most strikingly, compared with conventional DTIC-NPs, DTIC-NPs-DR5 mAb show significantly enhanced antitumor activity, increased cancer cell apoptosis, and decreased nonspecific toxicity. Therefore, a nanoparticulate system-carrying TMZ may target delivery to tumor cells, which enhances accumulation at the tumor site, helping to overcome medicine resistance, improve efficiency, and reduce non-tumor tissue toxicity (Figure 1).

As single agents and in combinations, numerous cytotoxic agents have been evaluated for treating metastatic melanoma, but none has ever demonstrated a survival advantage. Nevertheless, several chemotherapy regimens are often used in advanced disease, including DTIC and TMZ.
thus has potential advantages over DTIC in terms of convenience. TMZ is at least as effective against melanoma as DTIC and there is no significant difference in toxicity between the two agents. However, the HRQL following TMZ is better than that following DTIC, and it can cross the BBB; however, the incidence of lymphopenia following TMZ is higher, and it costs more. The financial resources and preferences of a patient should be taken into account when the patient is presented with chemotherapy. Liu et al. found that 90% of patients with incurable cancer preferred oral chemotherapy if there was demonstrated equivalence in terms of safety and efficacy. Therefore, TMZ can be used as the first-choice treatment for patients with malignant melanoma who live in remote areas or who have difficulty traveling to cancer centers for intravenous chemotherapy; are concerned about intravenous chemotherapy or have had difficulties with it; or who wish to receive treatment outside the clinic. However, such patients must have adequate financial resources. We will continue to administer DTIC to patients who do not have special requirements because there is no evidence that TMZ is superior; it is also more expensive. TMZ should be used as a first-line option for patients with brain metastases from malignant melanoma because it can enter the CNS, although there are no definite conclusions regarding its effectiveness in brain metastasis of melanoma.

TMZ is the first new chemotherapy agent in more than 30 years to receive approval for treating high-grade malignant gliomas. It is effective against primary brain tumors, and for this reason, is also being actively investigated for the treatment of secondary CNS malignancies, particularly in metastatic melanoma. Many retrospective studies have demonstrated the efficacy of TMZ in melanoma with brain metastases. Nevertheless, Chiorion-Sileni et al. showed that following the substitution of a DTIC-based regimen with a TMZ-based regimen, the incidence of CNS failures in metastatic melanoma was not significantly reduced and the clinical course was not modified. The authors believed that the main reason for this was the low systemic activity of TMZ, as well as all chemotherapy combinations in metastatic melanoma. Thus, there is a need for new drugs with greater systemic activity and that can cross the BBB to decrease CNS progression in melanoma patients.

Major advancements in the treatment of metastatic melanoma were recently achieved following the US Food and Drug Administration approval of the cytotoxic T-lymphocyte antigen 4-blocking monoclonal antibody ipilimumab and the BRAF V600E kinase inhibitor vemurafenib. These new drugs represent a shift away from treatment with cytotoxic agents and show promise in treatment of the disease. However, treating metastatic melanoma remains challenging because it is difficult to obtain long-term clinical benefits, even with the novel approved drugs. Chemotherapy remains an essential palliative treatment option of patients with metastatic melanoma, although it has not demonstrated overall survival benefit. Therefore, overcoming TMZ resistance and increasing its efficacy against malignant melanoma carries great importance. Nanocarriers play an increasingly important role in targeted therapy, and more effective and less harmful new drugs should be formulated.

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