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Evidence-based Series #8-4: Section 1

Temozolomide for the Treatment of Metastatic Melanoma: A Clinical Practice Guideline

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Question

1. What is the role of single-agent temozolomide in the treatment of patients with metastatic melanoma? Outcomes of interest include response rate, disease-free survival, overall survival, quality of life, and adverse effects.
2. Does the addition of interferon-alpha to temozolomide improve the disease-free survival, overall survival, or response rates compared to single-agent temozolomide?
3. Does the addition of thalidomide to temozolomide improve the disease-free survival, overall survival, or response rates compared to single-agent temozolomide?

Target Population

The recommendations apply to adult patients with unresectable metastatic malignant melanoma.

Recommendations

- It is reasonable to use temozolomide at a dose of 200 mg/m² orally for five days every four weeks as initial systemic treatment for patients with unresectable metastatic malignant melanoma.
- The addition of moderate-dose interferon-alpha 2b has produced a significantly higher response rate than single-agent temozolomide in a large randomized phase III study. However, overall survival was not altered and grade 3 and 4 hematologic toxicities were higher with the combined treatment. At the present time, the addition of interferon-alpha to temozolomide is not recommended.
- One randomized phase II study and six phase II studies have shown encouraging response rates when thalidomide is combined with temozolomide. However, dosing schedules of temozolomide in those studies differed from conventional prescribed doses and schedules. It is not clear whether the improved response rates were due to the small number of patients in the studies, the different dose schedules of temozolomide, or the addition of thalidomide. Further phase III studies are required to confirm whether there is a benefit associated with

the combination of temozolomide and thalidomide. Therefore, it is not recommended that thalidomide be combined with temozolomide at this time.

Qualifying Statements

- Dacarbazine is the only chemotherapy drug currently approved for the treatment of patients with metastatic malignant melanoma, with response rates ranging from 6% to 15% observed in large randomized trials. Virtually all responses are partial, with median durations of response of only seven to eight months. Given these overall disappointing results, there is consensus among most physicians treating patients with metastatic malignant melanoma that it is appropriate to recommend more convenient treatments or experimental treatments to these patients.
- Due to oral dosing, temozolomide is a reasonable choice, particularly for patients who would have difficulty travelling to cancer centres for intravenous chemotherapy.
- Temozolomide has demonstrated an efficacy equal to that of dacarbazine in a randomized phase III trial. However, unlike dacarbazine, temozolomide is a convenient oral treatment that penetrates the blood-brain barrier and has shown activity against brain metastases. Although surgery is the preferred treatment modality for patients with solitary brain metastases from melanoma, temozolomide is the preferred chemotherapy for patients with brain metastases who require systemic treatment.

Key Evidence

- Two randomized controlled trials, three randomized phase II trials, and 21 single-arm phase II and I trials were reviewed.
- One randomized controlled trial comparing temozolomide with intravenous dacarbazine was located. Response rates and overall survival were similar in the two groups. Progression-free survival was significantly prolonged with temozolomide (median 1.9 versus 1.5 months; $p=0.012$).
- A second randomized controlled trial compared temozolomide with temozolomide combined with interferon. Results from that trial indicate a significantly higher response rate with the combination treatment but no difference in overall survival. However, the difference in the time to the first formal disease assessment between arms may have influenced this difference. Grade 3 and 4 hematological toxicities were significantly higher in patients receiving the combination treatment.

Related Documents

The Program in Evidence-based Care's:

- Evidence-based Series Report #8-3: *Biochemotherapy for the Treatment of Metastatic Malignant Melanoma.*
- Evidence-based Series Report #8-5: *Single-agent Interleukin-2 for the Treatment of Metastatic Malignant Melanoma.*
- Evidence-based Series Report #8-6: *Management of Brain Metastases in Melanoma Patients*

Please note that these guidelines are currently under development and are not yet available on the CCO Web site.

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