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Is Temozolomide In Combination With Interferon Alpha-2b A Safe And Effective Treatment For Malignant Melanoma?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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Abstract

Objective: The objective of this selective EBM review is to determine whether or not temozolomide in combination with interferon alpha-2b a safe and effective treatment for malignant melanoma.

Study Design: Review of three randomized controlled trials published in the United States and Britain between 2003 and 2005.

Data Sources: Three non-blind randomized controlled trials were found via Cochrane library and PubMed.

Outcomes Measured: Efficacy was measured by survival greater than or equal to 12 months, with one (experimental) group receiving treatment with oral temozolomide (TMZ) and subcutaneous interferon alpha-2b (IFN-∝2b) and the other (control) group receiving oral TMZ alone. Safety was measured by rates of nausea with the same experimental and control groups. Safety was also measured by adverse event rates, with one group receiving combination treatment with IFN-∝2b in a body surface area-based (BSA) dose, and the other group receiving combination treatment with IFN-∝2b in a fixed dose.

Results: Kaufman et al and Danson et al demonstrated increased survival at 12 months when comparing treatment with TMZ + IFN-∝ to TMZ monotherapy (ABI 9.7% and 8%, respectively). Danson et al also found increased rates of nausea with combination treatment compared to TMZ alone (ARI 11%, NNH 10). Ritchtig et al showed a slightly increased rate of adverse events with an increased dose of IFN-∝2b when combined with TMZ (ARI 1.1%, NNH 90). No statistical analyses were performed on the data.

Conclusions: Based on these results, it is inconclusive if TMZ + IFN-∝2b is a safe and effective treatment for malignant melanoma. Although results on survival suggest a benefit to combination treatment, statistical analysis is required. Results for safety demonstrated increased adverse event and nausea rates both with the addition of IFN-∝2b and at increased doses of IFN-∝2b, however small sample size and lack of statistical analysis make it difficult to assume the safety of combination treatment.

Key Words: temozolomide; interferon alpha-2b; malignant melanoma

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INTRODUCTION

Malignant melanoma is an aggressive cancer of melanocytes, the pigment-producing cells of the skin.[1] This paper evaluates three randomized, controlled trials (RCTs) comparing the safety and efficacy of temozolomide (TMZ) in combination with interferon alpha-2b (IFN-∝2b) in the treatment of malignant melanoma.

Melanoma is the leading cause of death due to skin disease, accounting for more than 8,000 deaths per year.[2] The incidence of melanoma in the United States is increasing. The risk of developing the disease for a Caucasian man born in 2010 is 1 in 39, and 1 in 58 for a Caucasian woman.[3] This is compared to a 1 in 500 chance for an individual born in 1935.[3] In addition to the lives lost to this aggressive skin disease, its toll can be measured in the financial burden it carries. An individual who dies from melanoma loses an average of $413,000 in future earnings, which translates to a total loss of $3.5 billion in earnings per year due to melanoma death.[2] Additionally, an American loses 20.4 years of potential life due to a death from melanoma, compared to an average of 16.6 years from other malignancies.[2] This loss of potential life highlights the great need to improve the treatment of this disease.

In 2012 there were an estimated 76,250 cases of melanoma, accounting for 4% of cancers in men and 3% in women.[4] Both the commonness and the lethality of the disease highlight the importance to recognize and act upon its earliest signs. A pigmented lesion that is suspicious for malignant melanoma often have one or more of the "ABCDE" characteristics, which include asymmetry, irregular border, variegated color, diameter > 6 mm, and evolution. Identified risk factors include freckles, fair complexion, red or blond hair, blue eyes, family history of melanoma, the presence of multiple nevi, and those whose first sunburn occurred at an early

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age.[4] The single most important prognostic factor for a melanoma is the depth of skin that it penetrates. Ten year survival rate for a tumor that is < 1 mm thick is 95%, compared to 30% for tumors that penetrate > 4 mm.[4] Metastatic melanoma carries a 10% survival rate and has historically been resistant to chemotherapy.[4]

Melanoma is usually treated by local excision, with the addition of sentinel lymph node biopsy for tumors > 1 mm deep or with high risk histologic features.[4] For regional recurrences in extremities, isolated limb perfusion or melphalan and hyperthermia are used.[3] Dacarbazine is considered standard systemic chemotherapy and is associated with a 15% response rate.[4,5] High dose IFN-∝2b is also utilized but is associated with high toxicity.[4]

TMZ is an oral compound which shares an active breakdown product with dacarbazine.[5] TMZ advantages over dacarbazine include better absorption when taken orally, and better penetration in all tissues of the body since it does not require enzymatic activation in the liver.[5] TMZ also has demonstrated better response in treating brain metastases due to its ability to penetrate the blood-brain barrier.[5] This is an important feature due to the propensity for melanoma to metastasize to the brain. IFN-∝2b has been used in combination with dacarbazine in the past and has shown improved tumor response rates but has not shown an increase in survival.[4]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not temozolomide in combination with interferon alpha-2b is a safe and effective treatment for malignant melanoma.

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METHODS

Adult men and women between the ages of 18 and 88 with malignant melanoma were included in all three studies. Interventions studied were the use of TMZ in combination with INF-∝2b. Comparisons were made between TMZ alone and TMZ in combination with IFN-∝2b in a fixed (rather than BSA-based) dose. Outcomes measured were survival greater than or equal to one year, rates of nausea, and adverse drug event rates. All three studies were randomized, controlled trials.

All articles were published in peer-reviewed journals and were originally published in English. Articles were researched via Cochrane library and PubMed using key words "temozolomide interferon alpha melanoma". Articles were selected based on relevance to my clinical question and if they reported patient-oriented outcomes. Inclusion criteria were if studies were randomized, controlled trials published between 1999 and the present. Exclusion criteria were if patients were under 18 years of age. Statistics reported include RRI, ARI, NNH, RBI, ABI, and NNT. Table 1 describes the demographics and characteristics of each study.

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Table 1. Demographics & characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Danson et al[5] (2003)	RCT	181	18-88	- Advanced metastatic melanoma - No previous chemotherapy - Full recovery from previous therapy - Adequate bone marrow reserve (neutrophils ≥ 1,500/µL; platelets ≥ 100,000 µ/L, Hgb ≥ 10g/dL) - Urea and creatinine < 1.5 x the upper limits of laboratory normal (ULN) - Adequate hepatic function (total bilirubin < 1.5 x ULN, AST < 3 x ULN, alkaline phosphatase ≤ x ULN - Adequate birth control measures	- Pregnant or nursing - Uncontrolled vomiting that would interfere with administration of oral medication - biological therapy within 4 weeks of administration of temozolomide - If known HIV + - Clinically significant comorbidity that would interfere with study evaluations	4	Experimental: oral temozolomide 200 mg/m^2 PO qd x 5d with IFN-∝2b 5 mIU SQ every MWF; Treatment cycles repeated every 28 days VS Control: temozolomide PO 200 mg/m^2 at 8-hour intervals for a total of five doses, repeated every 28 days
Kaufman et al[6] (2005)	RCT	294	18-75	- Melanoma stage IV with no prior systemic therapy in stage IV - Karnofsky performance status ≥ 60% - WBCs > 3,000/mm^2, platelets >100,000, serum creatinine < 2x ULN, bilirubin < 1.5 mg/dL - Prior treatment (adjuvant, stage III) had to be completed at least 4 weeks before study	- Evidence of CNS metastases - Major concomitant illness of cardiovascular, respiratory, or renal system - Pregnant or nursing - Primary ocular or mucosal melanoma - Nonmeasurable disease	23	Experimental: oral temozolomide 200 mg/m^2/day, days 1-5 every 28 days, in combination with subcutaneous IFN-∝2b 5 mU/m^2; days 1, 3, and 5 every week VS Control: Oral temozolomide (same dose) alone
Ritchtig et al[7] (2004)	RCT	47	37-74	- Stage IV metastatic melanoma that is surgically incurable - Eastern Cooperative Oncology Group performance status of 0-2 - Adequate organ function: Hgb ≥ 10g/dL, serum creatinine < 1.5 x upper limit of normal range (ULN), leukocytes > 3,000 g/L, platelets > 100,000 g/L, liver function < 3 x ULN, alkaline phosphatase < 3 x ULN, bilirubin < 2 x ULN - Life expectancy > 12 weeks	Not indicated	0	Experimental: temozolomide 150 mg/m^2 days 1-5 PO every 28 days with IFN-∝2b 10 MIU/m^2 every other day VS Control: temozolomide 150 mg/m^2 on days 1-5 every 28 days with IFN-α2b in a fixed dose of 10 mIU every other day

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OUTCOMES MEASURED

All outcomes measured were patient-oriented evidence that matters (POEMs). Danson et al and Kaufman et al measured survival greater than or equal to 12 months.[5,6] The amount of people in each group still living after 12 months were counted and reported as a percentage. Adverse events were also studied. Ritchtig et al measured adverse drug events, including neurological symptoms, drug-induced skin eruption, sepsis, and brain hemorrhage.[7] Patients reported any adverse events that they experienced during the course of treatment, and adverse events were differentiated from common side effects such as nausea, vomiting, arthalgia, myalgia, and headache. Danson et al measured the most common side effect of nausea.[5] Patients who reported nausea during the course of treatment were recorded and counted as a percentage of the total population studied.

RESULTS

Three randomized controlled trials that reported dichotomous data were used in this review. Two trials studied the combination of TMZ with IFN-∝2b compared to the use of TMZ alone.[5,6] One study analyzed the use of TMZ with IFN-∝2b in a BSA-based dose compared to fixed dosing.[7] Dosages of TMZ varied from 150 mg/m^2 to 200 mg/m^2, and it was given once daily orally for five days once per 28-day cycle. TMZ dose frequency differed in the control group of Danson et al in which it was given every 8 hours for a total of 5 doses for every 28-day cycle.[5] Dosages of IFN-∝2b ranged from 5 milliunits/m^2 (mU/ m^2) subcutaneously on days one, three, and five to 10 million international units (mIU) subcutaneously on days one, three and five. All three studies utilized 28-day treatment cycles.

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All studies required patients to have stage IV melanoma, however Kaufman et al excluded patients who had metastases to the central nervous system.[6] Both Kaufman et al and Danson et al indicated that their patients must not have received previous chemotherapy for their disease in Stage IV, however Ritchtig et al did not make this specification.[5,6,7] The study by Kaufman et al was performed in an outpatient setting, while Ritchtig et al and Danson et al did not specify whether their studies were performed on an outpatient or inpatient basis.[5,6,7] The number of patients that withdrew from each study is indicated in Table 1.

In the study by Kaufman et al, the intent to treat population was made up of 280 patients, 139 in the TMZ arm, and 143 in the TMZ + IFN-∝2b arm.[6] Of the intent to treat population, 35 patients in the TMZ + IFN-∝2b group demonstrated either complete or partial response, compared to 18 patients in the TMZ group.[6] Partial or complete response was defined as remission or >50% decrease in disease bulk as measured by physical exam, CT, or MRI.[6] These measurements were performed before treatment and after every second cycle. Of these individuals who demonstrated either partial or complete response, 17 of 35 patients in the TMZ + IFN-∝2b group (48.6%) survived longer than 12 months, compared to TMZ alone where 7 of 18 patients (38.9%) survived longer than 12 months.[6] This translated to a relative benefit increase (RBI) of 24.9%, an absolute benefit increase of 9.7%, and a number needed to treat (NNT) of 11(Table 2). No statistical tests were performed on this data.

Danson et al measured one-year survival rates out of the total intent to treat population.[5] Of those who received TMZ alone, 18% were alive at 12 months, compared to 26% of the group who received TMZ + IFN-∝2b.[5] This translated to a RBI of 44.4%, an ABI of 8%, and an NNT of 13 (Table 2). No statistical tests were performed on this data.

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Table 2. Survival greater than or equal to 12 months

Study	TMZ alone	TMZ + IFN-A2B	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
Kaufman et al	38.9%	48.6%	24.9%	9.7%	11
Danson et al	18%	26%	44.4%	8%	13

Ritchtig et al noted the number of patients who experienced adverse drug events. For this study it is important to differentiate adverse drug events, in which a patient is harmed by the drug, from common side effects such as nausea, vomiting, arthralgia, and fatigue. Of the group that received TMZ + IFN-∝2b in a BSA-based dose (control), 2 out of 20 experienced adverse drug events, which included sepsis and brain hemorrhage.[7] Of the group that received TMZ + IFN-∝2b in a fixed dose (experimental), three out of 27 experienced adverse drug events, which included two patients with neurological symptoms and one with a drug-induced skin eruption.[7] Ritchtig et al does not indicate the severity nor the outcome of these events, nor does he perform statistical tests to indicate if any significant difference was observed between the two groups. These data translate to a relative risk increase (RRI) of 11.1% of a fixed versus weight-based dose, an absolute risk increase (ARI) of 1.1%, and a number needed to harm (NNH) of 90 (Table 3). Referencing the dosages of each group from Table 1, it should be noted that the fixed dose of IFN-∝2b for the experimental group of 10 mIU is far lower than the weight-based dose of the control of 10 MIU/m^2. Therefore the lower dosage of the control group is associated with fewer adverse events.

The most common side effect reported in Danson et al was nausea.[5] Nausea, in part, represents the toxicity that the drug treatment regimen had on the patients, and is important to

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take note of because it influences the quality of life of these critical patients. In the group that received TMZ alone, 39% experienced nausea, compared to 49% of those who received TMZ + IFN-∝2b.[5] This correlates with a RRI of 28.5%, ARI of 11%, and a NNH of 10 (Table 3).

Table 3. Adverse drug events and side effects

Outcome	Control event rate	Experimental event rate	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
Adverse drug events	0.10	0.111	11.1%	1.1%	90
Nausea	0.39	0.49	28.9%	11%	10

DISCUSSION

Based on the results for survival at or greater than 12 months from Kaufman et al and Danson et al (Table 2), one can see a modest increased benefit in the combination treatment of TMZ and IFN-∝2b as opposed to using TMZ alone. Neither of the studies performed statistical analyses on this particular data and therefore it is unknown if these findings are statistically significant.

Analyzing the calculated NNT is perhaps the best way for both patients and academics alike to appreciate the true benefit, or lack thereof, of the treatment of interest. The results from Kaufman et al and Danson et al showed a NNT of 11 and 13, respectively, meaning that for every 11-13 patients treated with the regimen of interest, one patient would benefit in the form of surviving greater than or equal to 12 months. Although the NNT are relatively low, it is more accurate to interpret the data in the context of the quality of the life that the addition of IFN-∝2b is adding for these patients. The patients participating in these studies have stage IV melanoma,

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which historically has been resistant to chemotherapy, and carries about a 10% survival rate.[4] The poor survival rate highlights the importance of considering the adverse effects that these drugs have in the interest of quality of life.

The rate of adverse events studied by Ritchtig et al resulted in a NNH of 90 (Table 3). A high NNH translates to a low risk of harm, however, this number in this context is misleading for two reasons. For one, the severity of the adverse events varies greatly. These events ranged from sepsis and brain hemorrhage in the control group to neurological symptoms and drug-induced skin eruption in the experimental group. The outcomes of these adverse events are not discussed. Secondly, this measurement has a very small sample size of 47 patients total. The combination of the wide range of adverse events and the small sample size makes it difficult to ascertain from this data whether the addition of IFN-∝2b to TMZ is safe in the treatment of stage IV melanoma.

Danson et al observed an ARI in nausea of 11% with the addition of IFN-∝2b to TMZ treatment. Statistical tests were not performed on the data, however with a NNH of 10 (Table 3), one can ascertain that the combination treatment is associated with an increased risk of nausea. This plays a role in the quality of life of the patients and should be taken into consideration when choosing treatment options.

All of the studies included had limitations that should be discussed. For one, none of the trials were blinded, which allows the potential for bias to be introduced into the study. Additionally, Ritchtig et al had a relatively small sample size, with 20 patients in his control group and 27 in the experimental.[7] Kaufman et al excluded patients that had metastases to the central nervous system,[6] however one of the advantages of using TMZ over dacarbazine is that it

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is able to penetrate the blood-brain barrier,[5] and therefore perhaps its full effects were not observed.

TMZ is an oral drug that is nonenzymatically converted into its active form and is able to penetrate the blood-brain barrier.[5] It exerts its effects by DNA alkylation, which leads to breaks in the DNA strands and apoptosis.[8] It is widely used in the Unites States as an antineoplastic agent for conditions such as glioblastoma multiforme, cutaneous T-cell lymphoma, melanoma, Ewing sarcoma, and anaplastic astrocytoma.[8] Warnings exist for its potential to cause myelosuppression, nausea and emesis, hepatotoxicity, *Pneumocystis jirovercii* pneumonia, and rarely, secondary malignancies.[8]

IFN-∝2b is commonly used as an antineoplastic agent, biological response modulator, or immunomodulator for conditions such as hairy cell leukemia, lymphoma, melanoma, Kaposi sarcoma, chronic hepatitis B and C, and condyloma acuminata.[9] U.S. Boxed Warnings exist due to its potential to cause or aggravate neuropsychiatric disorders, autoimmune disease, infectious disorders, and ischemic disorders.[9] The wide range of adverse effects that is associated with IFN-∝2b may potentially limit its use.

CONCLUSION

It is difficult to definitively conclude whether the benefits of treatment with TMZ + IFN-∝2b outweigh the risks. Although the combination treatment in both Kaufman et al and Danson et al yielded improved survival, no statistical tests were performed on these results in order to determine if there was a significant difference between groups.[5,6] The studies also demonstrated increased rates of adverse effects with combination treatment, but of unknown statistical significance. Therefore further research should be aimed at determining the statistical

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significance of survival outcomes and rates of adverse effects in combination treatment of TMZ and IFN-∝2b versus TMZ alone. Additionally, since a major advantage of TMZ over dacarbazine, which is the current standard chemotherapy, is its ability to penetrate the blood-brain barrier,[5] further study should be aimed toward the effect of TMZ on patients with brain metastases. This is particularly important due to the propensity of melanoma to metastasize to the brain. The addition of more research, however, will not replace the importance of the personal choice to undergo intensive treatment, but it will hopefully help guide families to make the most educated decision possible.

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References

1. Urba WJ, Washington CV, Nadiminti H. Chapter 87. Cancer of the Skin. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. *Harrison's Principles of Internal Medicine, 18e.* New York, NY: McGraw-Hill; 2012.http://accessmedicine.mhmedical.com/content.aspx?bookid=331&Sectionid=40726823. Accessed October 01, 2014.

2. Ekwueme DU, Guy GP Jr, Li C, Rim SH, Parelkar P, Chen SC. The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-united states, 2000 to 2006. *J Am Acad Dermatol*. 2011;65(5 Suppl 1):133-143.

3. Geller AC, Swetter S. Screening and early detection of melanoma. August 26 2014; Topic 4845(Version 30.0). http://www.uptodate.com.ezproxy.pcom.edu:2048/contents/screening-and-early-detection-of-melanoma?source=machineLearning&search=melanoma&selectedTitle=1~150&sectionRank=2&anchor=H15#H18038394. Accessed September 26 2014.

4. Berger TG. Chapter 6. Dermatologic Disorders. In: Papadakis MA, McPhee SJ, Rabow MW. eds. *CURRENT Medical Diagnosis & Treatment 2014.* New York, NY: McGraw-Hill; 2014. http://accessmedicine.mhmedical.com/content.aspx?bookid=330&Sectionid=44291008. Accessed October 01, 2014.

5. Danson S, Lorigan P, Arance A, et al. Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. *J Clin Oncol*. 2003;21(13):2551-2557. doi: 10.1200/JCO.2003.10.039.

6. Kaufmann R, Spieth K, Leiter U, et al. Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: A randomized, phase III, multicenter study from the dermatologic cooperative oncology group. *J Clin Oncol*. 2005;23(35):9001-9007. doi: 10.1200/JCO.2005.01.1551.

7. Richtig E, Hofmann-Wellenhof R, Pehamberger H, et al. Temozolomide and interferon alpha 2b in metastatic melanoma stage IV. *Br J Dermatol*. 2004;151(1):91-98. doi: 10.1111/j.1365-2133.2004.06019.x.

8. Temozolomide (lexi-drugs). Lexi-Comp Online Website. http://online.lexi.com.ezproxy.pcom.edu:2048/lco/action/doc/retrieve/docid/patch_f/7732#. Published May 2014. Updated 2014. Accessed 11/30, 2014.

9. Interferon Alfa-2b (Lexi-Drugs). Lexi-Comp Online Website. http://online.lexi.com.ezproxy.pcom.edu:2048/lco/action/doc/retrieve/docid/patch_f/7090#war. Accessed 11/30, 2014.

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