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Clinical and Laboratory Investigations

Temozolomide and interferon α2b in metastatic melanoma stage IV

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Summary

Background A multicentre, centrally randomized, open-labelled study with temozolomide and interferon (IFN)-α2b was carried out to study the therapeutic effect in patients with metastatic melanoma stage IV.

Objectives The response rate, efficacy, side-effects, reasons for discontinuation of therapy and survival rate of 47 patients treated with temozolomide in combination with two different dosing regimens of IFN-α2b were documented.

Patients/methods Twenty-nine male and 18 female patients (mean age 57·6 years, range 34–74) were centrally randomized to two different arms: 20 patients received a treatment schedule with temozolomide 150 mg m^{-2} on days 1–5 orally every 28 days in combination with IFN-α2b 10 MIU m^{-2} every other day and 27 patients received temozolomide 150 mg m^{-2} on days 1–5 every 28 days in combination with IFN-α2b in a fixed dose of 10 MIU every other day.

Results We observed an overall response rate of 27·6% comprising five complete remissions (10·6%: one patient group A, four patients group B), in two of these five patients at the last follow-up in the study (4·3%, both in group B); and eight partial remissions (17%: six patients in group A, two patients in group B), in three of these eight patients at the last follow-up in the study (6·4%, two patients in group A, one patient in group B). Three patients showed stable disease (6·4%: one patient in group A, two patients in group B). Mean survival was 14·5 months [95% confidence interval (CI) 10–19] with no significant differences between treatment groups. However, there was a significant correlation with response after three cycles (log rank test, $P < 0{\cdot}03$). Within the 32 patients who completed at least three cycles of therapy, seven patients (three in group A and four in group B) with a partial or complete response showed a significantly better mean survival of 30·6 months (95% CI 19·1–42) compared with 25 patients who did not respond (13·7 months 95% CI 9·2–18·3). In total, patients with at least one complete remission showed the longest

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survival (37·1 months 95% CI 26·3–47·9), followed by patients with at least one partial response (17·4 95% CI 10·9–23·9). Major side-effects of the treatment were nausea, vomiting, headache, leucopenia, thrombopenia, elevation of liver function parameters and neurological symptoms. In five patients, the side-effects led to a discontinuation of treatment: neurological symptoms (two patients), sepsis (one patient), brain haemorrhage (one patient) and exanthema (one patient). There were no treatment-related deaths.

Conclusions The combination of temozolomide and IFN-α2b can easily be administered and shows tolerable toxicity. When an objective response occurs after three cycles, it indicates a significant survival advantage.

Key words: interferon α2b, metastatic malignant melanoma, temozolomide

Melanoma incidence is continuously increasing in Austria. At the Department of Dermatology, University of Graz, Styria, Austria, 80 newly diagnosed patients with melanoma were treated in 1981, 250 in 1991 and 398 in 2001.[1] This corresponds to annual incidences in Styria of 6·7 per 100 000 in 1981 and 33·1 per 100 000 in 2001 [95% confidence interval (CI) 29·92–36·51].[2] The number of patients with metastatic disease increased from six in 1981 to 74 in 2001. Forty-four of the patients died of their disease in 2001.

In stage IV disease (any T, any N, M1–M3)[3] median survival is very poor, despite various treatment options, ranging from 3·6 to 11·8 months.[4,5]

The most prescribed monochemotherapy in this stage is dacarbazine with a response rate between 10% and 33%.[6–11] A large variety of cytotoxic agents such as fotemustine, carmustine, cisplatin, carboplatin, vindesine, cyclophosphamide, vinblastine, lomustine, vincristine, hydroxyurea, bleomycin, paclitaxel and tamoxifen have shown an effect in metastatic disease with response rates between 2·5% and 47%[11] but so far, no therapy protocol has been proven to be superior concerning the survival of the patients.[12] It remains a matter of debate whether the combination of several cytotoxic agents may increase response rate or survival, but combined chemotherapy is definitely more toxic.[9,11,13–19]

A new alkylating drug, temozolomide, is an imidazotetrazinone synthesized in 1984 by Stevens *et al.*[20] Its active metabolite is 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC); its cytotoxic effect is based on DNA alkylation.[21–23] Whereas dacarbazine requires a liver passage for activation, temozolomide undergoes spontaneous hydrolysis to the active compound MTIC at the physiological pH of blood and tissues.[22] The bioavailability of the drug by oral administration is nearly 100% and, in contrast to dacarbazine, temozolomide penetrates the blood–brain barrier.[21,23–27]

Several studies with temozolomide have been performed and the substance has shown equal response rates to dacarbazine.[24–26,28] A phase II study performed by the Hellenic Cooperative Oncology Group with the combination of docetaxel 80 mg m^{-2} intravenously on day 1 in combination with temozolomide 150 mg m^{-2} on days 1–5 orally every 4 weeks revealed an overall response rate of 27% in 62 patients treated.[25] A randomized phase III study of oral temozolomide 200 mg m^{-2} on days 1–5 every 28 days vs. intravenous dacarbazine 250 mg m^{-2} on days 1–5 every 21 days revealed nearly the same response rates between the two arms (13·5% and 12·1%, respectively), with nearly equal side-effects.[24]

Interferon (IFN)-α2b is the most prescribed cytokine in metastatic disease and when used as monotherapy has shown lower response rates than dacarbazine (0–29%),[11] whereas the combination of dacarbazine and IFN-α showed higher response rates of 16–53%.[8,29–31]

In 1997 Kirkwood *et al.*[32] presented a phase I study to determine the maximal tolerated dose and the dose-limiting toxicity of temozolomide in weekly dosages of 750 mg m^{-2} or 1 g m^{-2} every 28 days in combination with escalating dosages (from 5 to 10 MIU m^{-2}) of IFN-α2b given subcutaneously three times a week in metastatic melanoma. In this study they observed an overall response rate of 25% (three of 12 complete and partial responses and four of 12 stable diseases). A recently published study by Agarwala and Kirkwood[33] in patients with stage IB–IV (eight patients stage IV) with two different cohorts of patients in this combination (cohort 1: temozolomide 750 mg m^{-2} weekly every 28 days and IFN-α2b in escalating dosages between 5 and 10 MIU m^{-2} daily

three times a week subcutaneously; cohort 2: temozolomide 1 g m^{-2} weekly every 28 days and IFN-α2b 5 MIU m^{-2} daily three times a week subcutaneously) showed that the pharmacokinetics of temozolomide were not affected by the coadministration of IFN-α2b. The authors observed an overall response rate of 17% including one complete remission and three partial remissions. In this study the maximal tolerated dose was either temozolomide 750 mg m^{-2} weekly plus IFN-α2b 7·5 MIU m^{-2} three times weekly or temozolomide 1 g m^{-2} plus IFN-α2b 5 MIU m^{-2} three times weekly.[33]

In our study we focused on the combination of temozolomide 150 mg m^{-2} on days 1–5 every 28 days (750 mg m^{-2} weekly) in combination with IFN-α2b in two dosages: 10 MIU m^{-2} three times weekly subcutaneously or 10 MIU three times weekly subcutaneously and studied the overall response rate as the primary outcome measure and the tolerability, side-effects, reasons for discontinuation of therapy, clinical outcome and survival rates of the treated patients as secondary measures.

Patients and methods

Study

The study was a multicentre open-labelled centrally randomized study, approved by the Ethics Committee of every centre. The primary endpoint of the study was overall response and the secondary endpoints were time to progression and survival.

Centres

Ten Austrian centres participated in this study – nine dermatology units and one internal medicine unit.

Patients

Patients, aged 19–75 years with stage IV melanoma (any T, any N, M1–M3),[3] surgically incurable and with measurable disease, were recruited into the study from July 1997 until March 2000. The patients had to have an Eastern Cooperative Oncology Group performance status of 0–2 with adequate organ function [haemoglobin ≥ 10 g dL^{-1}, serum creatinine ≤ 1·5 × ULN (upper limit of normal range), leucocytes ≥ 3000 g L^{-1}, platelets ≥ 100 000 g L^{-1}, liver function ≤ 3 × ULN, alkaline phosphatase ≤ 3 × ULN, bilirubin ≤ 2 × ULN] and life expectancy > 12 weeks. In all patients age, sex, location of metastases, response after three cycles, duration of therapy, rate and reasons for dropout, death due to melanoma and overall survival were recorded. All patients gave informed written consent.

Mode of treatment arms

Twenty patients were assigned to arm A (42·6%) and 27 to arm B (57·4%) using a stratified central telephone randomization procedure provided by the sponsor. Patients in arm A received temozolomide (Temodal®, AESCA, Traiskirchen, Austria) 150 mg m^{-2} daily orally on days 1–5 of each 28 days treatment cycle, in combination with IFN-α2b (Intron A®, AESCA) 10 MIU m^{-2} subcutaneously every other day. Patients in arm B received the same regimen of temozolomide but a fixed dose of 10 MIU every other day of IFN-α2b. Temozolomide doses were rounded to the nearest 20 mg to accommodate the capsule strength. Routine laboratory tests (haematological values, liver function, serum creatinine, alkaline phosphatase and bilirubin) were obtained before and after each treatment cycle and, if necessary, between cycles. Re-staging was performed after three cycles. In cases of progression, the treatment was discontinued; otherwise, treatment was continued for an additional nine cycles with re-staging after 6, 9 and 12 cycles.

Stratified randomization procedure of metastatic sites

It was recorded whether skin, lung, liver, brain, bone or other sites were involved by metastatic disease or liver metastases alone. The stratified assignment of patients to the study groups worked reasonably well and did not reveal significant differences according to centre ($P = 0{\cdot}857$) and metastatic site ($P = 0{\cdot}638$).

Statistical methods

The sample size of this study was prespecified with 50 patients per treatment group in order to detect a difference in overall response rate of 25%. Because this aim appeared to be unattainable, the study was stopped after the inclusion of approximately 50% ($n = 47$) of the patients. This truncation of the study reduced the statistical power to detect a difference of 25% from 82% to 39%. With this sample size only differences > 40% can be detected with acceptable statistical power (80%). Descriptive statistics such as absolute and relative frequencies, mean and standard deviations (range), as well as χ^2-test, Fisher's exact test, Student's

t-test or Mann–Whitney *U*-test were performed where appropriate. Time to progression and survival were analysed using the Kaplan–Meier method, together with the log rank test. For a multivariate approach, Cox proportional hazard regression analysis was used. All statistical calculations were performed using the SPSS 10·0 statistical software package (SPSS Inc., Sunnyvale, Chicago, IL, U.S.A.). $P < 0·05$ was considered to indicate statistical significance. No corrections for multiple comparisons were applied. Only one confirmative statistical test was performed, that is the analysis of the primary endpoint using Fisher's exact test. Statistical analysis was performed according to the intention-to-treat principle.

Results

Response

We observed an overall response rate of 27·6% comprising complete remissions in five patients (10·6%: one patient group A, four patients group B), in two of these five patients at the last follow-up in the study (4·3%: both in group B); and partial remissions in eight patients (17%: six patients in group A, two patients in group B), in three of these eight patients at the last follow-up in the study (6·4%: two patients in group A, one patient in group B). Three patients showed stable disease (6·4%: one patient in group A, two patients in group B). Regarding overall response, there was no significant difference between the study groups ($P = 0·511$). From the total of 13 patients with at least one partial or complete response, seven patients (35%, 95% CI 15·39–59·22) were in group A and six (22·2%, 95% CI 8·62–42·26) in group B. Between the treatment groups, time to progression was statistically not significantly different ($P = 0·70$), mean time to progression was 124 days (95% CI 86·7–161·4).

The response after three cycles was not significantly influenced by mode of therapy ($P = 0·345$), although disease progression was twice as common in group B than in group A patients. However, this was not statistically significant.

Age

The mean age was 57·6 ± 11·5 years (range 34–74). The mean age was the same in both treatment groups (57·6 years) and did not differ with respect to discontinuation of therapy, mortality and response after three cycles. There was no correlation between age and duration of therapy or survival. Age did not influence survival in Cox analysis.

Sex distribution

There were 29 male and 18 female patients (61·7% and 38·3%, respectively). No significant relationship was found between sex and treatment group, reason for discontinuing therapy, overall mortality, response after three treatment cycles or overall survival (log rank test, $P = 0·69$). Therapy was more likely to be completed in female patients (22·2%) than in male patients (6·9%), but the difference was not significant ($P = 0·13$).

Metastatic sites

Liver metastases alone were present in five patients (10·6%), metastases of other localization in 42 patients (89·4%) (Tables 1 and 2). There was no influence of the metastatic site or the number of sites involved on rate and cause of discontinuation, duration of therapy, mortality and response after three cycles. Survival time was significantly associated with the number of metastatic sites ($P = 0·004$).

Treatment demographics

Thirty-two patients (68·1%) completed three cycles of treatment, but only six (12·8%) patients completed 12 cycles. Treatment was discontinued in 41 (87·2%) patients owing to tumour progression (22 patients), adverse drug events (five patients), patients' wishes (noncompliance) in five patients and protocol violation (three patients) (two patients did not take temozolomide in the prescribed way and one patient was > 70 years) (Table 3). Six patients died. The mode of therapy did not influence the rate of discontinuation in either group. However, there was a significant influence ($P = 0·028$) of the mode of therapy on the reason for stopping therapy, as all cases of patient noncompliance were found in group A.

Table 1. Metastatic sites

No. of sites involved	Group A ($n = 20$ patients)	Group B ($n = 27$ patients)	Total
1	11	8	19
2	6	14	20
3	2	4	6
4	1	1	2

Table 2. Localization of metastatic sites

Metastatic site	Group A ($n = 20$ patients)	Group B ($n = 27$ patients)	Total
Lung	13	16	29
Liver	9	12	21
Bone	4	6	10
Brain	2	3	5
Skin	2	9	11
Suprarenal gland	1	2	3
Retroperitoneum	2	0	2

Table 3. Discontinuation of therapy

Reason	Group A ($n = 20$ patients)	Group B ($n = 27$ patients)
Tumour progression	8	14
Adverse drug event	2	3
Noncompliance	5	0
Protocol violation	2	1
Death	1	5
Completed protocol	2	4

Side-effects

The most common side-effects were nausea, vomiting, arthralgia, myalgia, headache, stomatitis, fatigue, flu-like symptoms, vertigo, constipation, diarrhoea, alopecia, paraesthesia, infection, leucopenia, thrombopenia, increased alkaline phosphatase, elevation of the liver function and hypertriglyceridaemia, all grade I–II. Seven patients had thrombopenia grade III, three had leucopenia grade III and three had hyperlipidaemia grade II. Five patients (10·6%) had adverse drug events: two patients with neurological symptoms and one patient with drug-induced skin eruption (all in group B); one with sepsis and one with brain haemorrhage (both in group A).

Duration of therapy

The mean duration of therapy was 124 ± 112 days (range 0–419). The duration of therapy did not differ significantly between the groups. The longest duration of therapy was in patients who had achieved a complete (266 days) or a partial (236 days) remission after three cycles, but this difference was not significant ($P = 0{\cdot}147$).

Survival time

Thirty-four patients (72·3%) died in the course of follow-up. Follow-up time was limited to a maximum of 43 months. Mean survival in all patients was 14·5 months (95% CI 10–19) with no significant differences between treatment groups (Fig. 1). However, there was a significant correlation with response after three cycles (log rank test, $P < 0{\cdot}03$). Of the 32 patients who completed at least three cycles of therapy, seven patients (three in group A and four in group B) with a partial or complete response showed a significantly better mean survival of 30·6 months (95% CI 19·1–42) in contrast to 25 patients who did not respond (13·7 months, 95% CI 9·2–18·3).

In total, patients with at least one complete remission showed the longest survival (37·1 months, 95% CI 26·3–47·9), followed by patients with at least one partial response (17·4 months, 95% CI 10·9–23·9). Patients without any remission had a mean survival of 8·1 months (95% CI 5·6–10·6). This was statistically significant ($P = 0{\cdot}002$).

In multivariate Cox proportional hazard regression analysis including the covariates age, sex, mode of therapy, pretreatment, time since first diagnosis and presence of metastases, response after three cycles remained significantly associated with survival ($P < 0{\cdot}001$).

Discussion

In this study we examined tolerability, remission rates and outcome in patients with metastatic melanoma stage IV treated with a combination of temozolomide and IFN-α2b, the latter in two different dosages. Our patient group showed a slight predominance of male patients, as is often found in series of patients with metastatic melanoma.[4,24,25,33–35] The mean age in our study was in the upper range (57·6 years) compared with many other studies,[4,5,12,13,24–26,33–37] ranging between 41 and 58·8 years.

In the literature, soft tissue metastases are most common, followed by lung, lymph node, brain and bone metastases.[4,15,24,34,35,38] The percentage of patients with liver metastases ranges between 20% and 39%.[4,24,25,34,35,38] Because this type of metastasis shows the lowest response rates in various palliative therapy regimens,[4,5,25,26] we decided to include the presence of liver metastases without any other metastatic deposits in the randomization procedure. However, exclusive involvement of the liver was a rare event seen only in five of our patients (10·6%).

Contrary to the phase I dose escalation study of Agarwala and Kirkwood,[33] in our study we had equal dosages of temozolomide with 150 mg m^{-2} in both

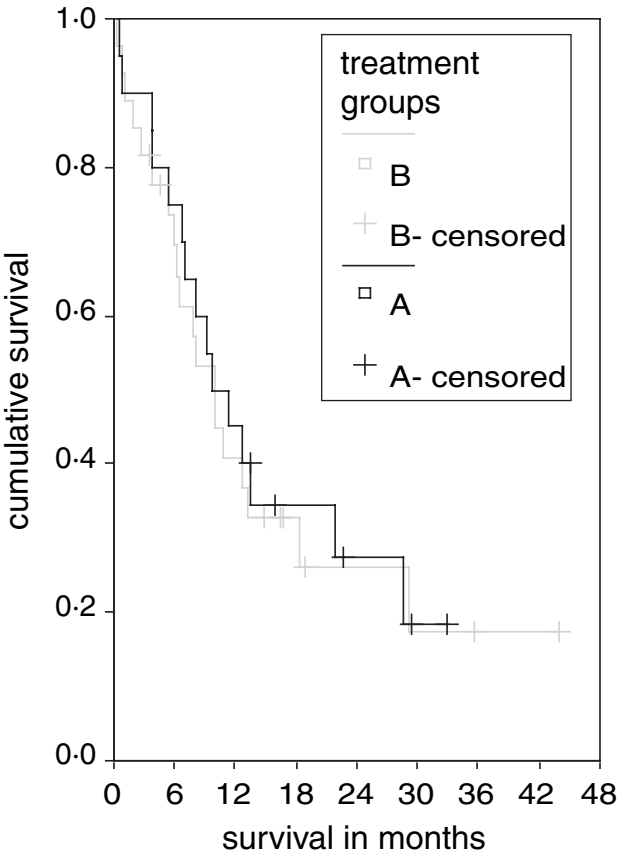

Figure 1. Kaplan–Meier plot according to treatment groups.

groups combined with a higher IFN-α2b dosage in group A with 10 MIU m^{-2} three times a week and a lower fixed IFN-α2b dosage in group B with 10 MIU three times a week.

The side-effects of temozolomide therapy are numerous, including leucopenia, thrombopenia, anaemia, nausea, vomiting, arthralgia, myalgia, constipation, increased alkaline phosphatase, fever, stomatitis, infection, skin rash, pruritus, diarrhoea, alopecia, disorder of taste and paraesthesia.[23–26,28,33] The common side-effects of IFN-α are flu-like symptoms, gastrointestinal symptoms, leucopenia, thrombopenia, myalgia, elevation of liver function tests, arthralgia and fatigue; rare are cardiac symptoms, neurological symptoms, depression, hypertriglyceridaemia, alopecia, thyroid autoantibodies, vertigo, bleeding diathesis, headache and vascular thrombosis.[33,39–45] In our patients we observed the same side-effects, at grades I–III. Five patients (10·6%) had adverse drug events.

The mean duration of therapy was 124 days (four cycles) (range 0–419 days), which is longer than the two to three cycles per patient noted in the literature.[24–26] The reasons for discontinuation of therapy in stage IV studies[24–26,33] are mostly disease progression and death, followed by noneligible patients and patients with serious adverse events, which was the same in our study.

In their study of patients with stage IB–IV disease, Agarwala and Kirkwood observed an objective response in four patients (17%) (one complete remission, three partial remissions) and four patients showed stable disease.[33] We found complete remissions in five patients (10·6%), partial remissions in eight patients (17%) and stable disease in three patients (6·4%), all stage IV disease. In previous studies of temozolomide without IFN in metastatic melanoma,[24–26,46] these figures ranged from 2·6% to 8% for complete remission, 8·7–19% for partial remission, and 14·3–23% for stable disease.

The median survival of patients with metastatic melanoma at distant sites is poor, ranging from 2 to 9 months.[6,7,12,47,48] Bleehen *et al.*[26] reported median survival of 5·5 months in temozolomide monotherapy. In a study performed by Middleton *et al.*[24] the median survival rate in the temozolomide-treated group was 7·9 months, and 5·7 months in the dacarbazine-treated group. The median survival of patients treated with temozolomide and docetaxel was 11 months in the study of Bafaloukos *et al.*[25] A published study of Frick *et al.*[46] with temozolomide administered in 19 of 23 patients as second-line therapy after chemo- and/or immunotherapy showed a median survival of 7 months. In the recently published study of Agarwala and Kirkwood with temozolomide and IFN combination therapy,[33] the median survival was 9 months. Our patients had a mean survival of 14·5 months (range 1–43), which is longer than in the other studies.

When the relationship between the response after 3 months and survival time was examined, 'responders' (complete or partial remission) showed a significantly longer survival than nonresponders and in multivariate Cox logistic regression analysis only the response after three cycles had significant influence on survival. The dosage of IFN-α2b did not influence survival or remission rate, either in univariate or multivariate analyses. As there has been no treatment arm without IFN, the actual role of IFN in addition to temozolomide remains to be determined.

In summary, the combination of temozolomide and IFN-α2b is easily administered and the lower IFN-α2b dosage is usually well tolerated and seems to have a positive effect on survival in patients with metastatic melanoma. The effect on survival can in part be predicted by the response rate after three cycles.

Acknowledgments

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