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Chemoimmunotherapy with dacarbazine, cisplatin, interferon-alpha2b and interleukin-2 *versus* two cycles of dacarbazine followed by chemoimmunotherapy in patients with metastatic melanoma: A randomised phase II study of the European Organization for Research and Treatment of Cancer Melanoma Group

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ABSTRACT

Background: Chemoimmunotherapy for patients with metastatic melanoma is associated with high toxicity, and only a subset of patients will benefit. This randomised phase II study was performed with the primary objective of exploring whether two cycles of dacarbazine monotherapy could select the subset of patients that would benefit most from more intensive chemoimmunotherapy.

Patients and methods: Patients with metastatic melanoma were randomised to either receive chemoimmunotherapy with dacarbazine, cisplatin, interferon-alpha and interleukin-2 (arm A) or initial treatment with two cycles of dacarbazine monotherapy followed irrespective of response by the same 4-drug regimen of chemoimmunotherapy (arm B). Chemoimmunotherapy was continued in the absence of disease progression for a maximum of four cycles. Primary end-point was the disease stabilisation rate.

Results: A total of 93 patients were randomised, and 89 patients were eligible. Disease stabilisation (complete/partial response or stable disease) was achieved in 19 patients (42.2%) in arm A and 9 patients (20.5%) in arm B. In arm B 32 of the 44 patients continued chemoimmunotherapy after two cycles of dacarbazine. Of 20 patients with progressive disease (PD) after two cycles of dacarbazine in arm B, only 2 patients achieved an objective response. Median overall survival (OS) in arms A and B was 10.5 months and 9.5 months, respectively.

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Conclusions: Despite a lower initial stabilisation rate, the strategy of starting with 2 courses of DTIC prior to a 4-drug regimen led to comparable median overall survival. Only few transient responses were achieved with the 4-drug regimen in patients with disease progression on DTIC, suggesting frequent cross resistance. Two cycles of dacarbazine monotherapy cannot be recommended to select patients for more intensive chemoimmunotherapy.

1. Introduction

The prognosis of patients with metastatic melanoma remains poor, with median overall survival times of around 9–11 months. The current reference treatment remains single agent dacarbazine, with response rates of approximately 15%. A benefit on overall survival has never been demonstrated.[1] Many efforts have been made to improve on these results. The combined use of chemotherapy and immunotherapy has attracted much interest given the high response rates in small phase II studies at a time when the results of randomised phase III studies of chemotherapy *versus* chemoimmunotherapy were not yet available. Our group, the European Organization for Research and Treatment of Cancer (EORTC) Melanoma Cooperative Group, had just finished the accrual of a randomised study of dacarbazine, cisplatin, interferon-alpha (IFN-α) with or without interleukin-2 (IL-2),[2] and two early conclusions were already possible. Firstly, chemoimmunotherapy regimens were accompanied by an increased toxicity compared to chemotherapy alone, and secondly, a significant part of patients would still not benefit from this treatment since more than one-third of patients discontinued treatment already after two cycles because of progressive disease (PD). We therefore were interested to answer the question whether patients who had a greater likelihood of responding to intensive chemoimmunotherapy could be identified.

This study was designed to evaluate the question whether it is possible to select patients for intensive chemoimmunotherapy by two cycles of dacarbazine monotherapy. This could imply that patients not responding to dacarbazine monotherapy would have a low probability of achieving a response on subsequent chemoimmunotherapy. The study was designed as a randomised phase II study of up to four cycles of chemoimmunotherapy *versus* two cycles of dacarbazine monotherapy followed irrespective of response by up to four cycles of chemoimmunotherapy.

2. Patients and methods

Eligibility criteria and schedule of chemoimmunotherapy have been described elsewhere.[2] Briefly, patients were eligible with histologically documented evidence of measurable metastatic cutaneous melanoma not amenable to curative surgery, age 18–70 years, Karnofsky performance status $\geqslant$60%, life expectancy $\geqslant$3 months, no prior therapy for metastatic disease with any of the study drugs, no chemotherapy $\leqslant$3 months prior to study entry, no second malignancy except for adequately treated basal cell carcinoma of the skin or carcinoma *in situ* of the cervix, no serious concomitant disease, no concomitant treatment with immunosuppressive drugs, normal hepatic and renal function.

Randomisation was performed centrally (EORTC Data Centre, Brussels). Patients were stratified according to the centre and level of serum LDH value ($\leqslant$upper normal limit (UNL) *versus* >UNL and $\leqslant$2 times UNL *versus* >2 times UNL)[3,4] and randomised into two treatment arms using the minimisation technique. Treatment in arm A consisted of cisplatin 30 mg/m^2 i.v. days 1–3, dacarbazine 250 mg/m^2 i.v. days 1–3, IFN-α 10 MU/m^2 days 1–5 s.c. and IL-2 i.v. 1 mg/m^2/6 h day 4, 1 mg/m^2/12 h/day 5, 1 mg/m^2/24 h day 6, 0.25 mg/m^2/24 h days 7–9, each cycle repeated every 4 weeks in the absence of disease progression for a maximum of four cycles. Treatment in arm B consisted of dacarbazine 850 mg/m^2 i.v. days 1 and 22 followed irrespective of response by a maximum of four cycles of cisplatin, dacarbazine, IFN-α and IL-2 as in arm A.

Evaluation of the disease was performed every two cycles according to World Health Organisation (WHO) criteria. In the case of disease stabilisation, defined as stable disease (SD), partial (PR) or complete response (CR) treatment was continued. Chemoimmunotherapy with the 4-drug combination was given for a maximum of four cycles. Dose reductions and delays were specified as per the protocol. Toxicity was scored according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC).

The primary objective of the study was the rate of stabilisation of the 4-drug chemoimmunotherapy regimen and of a regimen in which this was preceded by two cycles of dacarbazine monotherapy. Secondary end-points were tumour response and stabilisation rate after the 4-drug regimen, response duration, toxicity, progression-free survival and overall survival.

3. Statistical considerations

The Simon one sample two stage design was used. The following hypothesis was made: 20% is the largest stabilisation rate after four cycles which, if true, implies that the therapeutic activity does not warrant further investigation, 40% is the target stabilisation rate which, if true, implies that the therapeutic activity does warrant further investigation. The statistical errors were $\alpha = 0.10$, $\beta = 0.05$. The first test was performed after 21 patients had been randomised to each arm and were evaluable for stabilisation rate. If $\leqslant$3 stabilisations out of 21 patients were observed in arm B, the study was discontinued. In any other situation, the study was continued until 90 patients were evaluable for response, 45 in each arm after which a second test was performed. If $\leqslant$12 stabilisations out of 45 patients were observed in arm

B and >12 in arm A, the regimen of arm B would not be of further interest. If >12 stabilisations out of 45 patients were observed in each arm B, the regimen of arm B would be of further interest. In the unusual situation that ⩽12 stabilisations were observed in each arm, the patient characteristics should be closely evaluated in order to explain such a surprising outcome.

The overall survival (OS) was calculated from the date of randomisation until the date of death or last known to be alive (censored observation). Progression-free survival (PFS) was calculated from the date of randomisation until the date of progression or death; the follow-up of patients still alive and without progression was censored at the last date of examination/contact. Disease-free survival (DFS) was calculated from the date of CR/PR until progression.

Actuarial curves were calculated according to the Kaplan–Meier method, and the Greenwood formula was used to obtain the standard errors of the estimates at a given time moment.[5] The 95% confidence interval (CI) for the median was obtained using the reflected method.[6] All eligible patients who started the treatment allocated by randomisation were included in the statistical analyses. Being a phase II trial, no treatment comparisons have been performed and no *P*-values have been computed.

4. Results

Between April and December 2000, a total of 46 patients were randomised (22 in arm A and 24 in arm B). At the interim analysis, 5 patients had reached stabilisation in arm A and 4 patients in arm B. Therefore, the accrual was continued as planned. At full accrual (August 2002), a total of 93 patients were entered into the study. Patient characteristics are shown in Table 1. Eighty-nine patients were eligible, 45 in arm A and 44 in arm B. Reasons for ineligibility were site of primary, serious concomitant disease, non-measurable disease and stage of disease, each in one patient.

Table 1 – Patient characteristics

	Arm A (*n* = 45)	Arm B (*n* = 44)
Male/female	23/22	26/18
Age (median, range)	48 (21–69)	48 (19–67)
Karnofsky PS		
90–100%	41	41
70–80%	3	2
60%	1	1
Serum LDH		
<UNL	25	24
UNL – ⩽2x UNL	15	14
⩾2x UNL	5	6
AJCC stage		
M1a	1	3
M1b	7	5
M1c	37	36

UNL, upper normal limit.

4.1. *Adherence to treatment schedule*

The total number of cycles that were administered per patient is shown in Table 2. In arm A, 20 patients (44.4%) completed the four cycles of chemoimmunotherapy, whereas 25 patients (55.6%) discontinued treatment earlier because of PD in 18 (40%) and toxicity as a major reason in 7 patients (15.6%). In arm B 14 patients (31.8%) completed the six cycles of dacarbazine (two cycles) followed by chemoimmunotherapy (four cycles). Twenty patients (45.5%) discontinued treatment because of PD (9 patients during dacarbazine monotherapy), 5 patients (11.4%) because of toxicity (all during chemoimmunotherapy), 4 (9%) patients refused further treatment (2 during dacarbazine monotherapy) and 1 patient (2.3%) was lost to follow-up.

4.2. *Toxicities*

Toxicity occurred most frequently during chemoimmunotherapy, as expected. There were no major differences in the occurrence of toxicity between the two study arms when all cycles of treatment were considered. When only the first two cycles, i.e. chemoimmunotherapy *versus* dacarbazine were considered, there was a higher incidence in arm A for grade 3 fever without infection (13.6% *versus* 0%), grade 3 lethargy (25.0% *versus* 0%), grade 3 anorexia (22.7% *versus* 0%) and grade 3 vomiting (15.9% *versus* 2.3%). The most frequent grades 3–4 toxicities in arms A and B were fever without infection (22.8% and 20.5%, respectively), lethargy (29.6% and 25%), anorexia (22.7% and 18.2%) and vomiting (18.2% and 9.1%). One patient experienced a fatal cardiopulmonary arrest, and 5 patients had severe cardiac failure, myocardial ischaemia or infarction or grade 4 hypotension.

4.3. *Efficacy of treatment*

Efficacy results are summarised in Table 3. In arm A, 19 patients (42.2%) achieved at least disease stabilisation: 1 CR (2.2%), 9 PR (20%) and 9 SD (20%), and 26 patients (57.8%) had PD as best response. Overall in arm B, 9 patients (20.5%) achieved at least disease stabilisation: 2 CR (4.5%), 5 PR (11.4%) and 2 SD (4.5%), while 30 patients (68.2%) had PD.

After the initial two cycles of dacarbazine monotherapy, 9 patients (20.5%) had disease stabilisation (4 PR and 5 SD) and 35 patients (79.5%) had PD. Thirty-two patients (72.7%) in arm B were able to continue chemoimmunotherapy after the initial two cycles of dacarbazine. In these patients, the stabilisation rate was 28.1% (2 CR, 5 PR, 2 SD). Of the 21 patients with PD after

Table 2 – Total number of cycles in patients

Cycles (*n*)	Arm A (*n* = 45)	Arm B (*n* = 44)
1	8 (17.8%)	4 (9.1%)
2	12 (26.7%)	8 (18.2%)
3	5 (11.1%)	6 (13.6%)
4	20 (44.4%)	10 (22.7%)
5	n.a.	2 (4.5%)
6	n.a.	14 (31.8%)

n.a., not applicable.

Table 3A – Overall efficacy results

Best response	Arm A ($n = 45$)	Arm B ($n = 44$)
CR	1 (2.2%)	2 (4.5%)
PR	9 (20%)	5 (11.4%)
SD	9 (20%)	2 (4.5%)
PD	26 (57.8%)	30 (68.2%)
CR + PR	10 (22.2%)	7 (15.9%)
CR + PR + SD	19 (42.2%)	9[a] (20.4%)
95% CI	(27.7%, 57.9%)	(9.8%, 35.3%)

a After dacarbazine alone, 3 patients reached PR, 3 patients SD and 3 patients PD.

Table 3B – Overall response and initial response to DTIC in arm B

Best response	Overall response ($n = 44$)	Response to DTIC		
		PR	SD	PD
CR	2 (4.5%)	0	1	1
PR	5 (11.4%)	3	1	1
SD	2 (4.5%)	0	1	1
PD	35 (79.5%)	1	2	20
CR + PR	7 (15.9%)	3	2	2
CR + PR + SD	9 (20.4%)	3	3	3

two cycles of DTIC monotherapy and who received at least one cycle of chemoimmunotherapy, only 2 patients (9.5%, 95% CI 1.2–30.4%) achieved an objective response (1 CR and 1 PR). The total number of stabilisations observed ($N = 9$) was lower than the minimum one ($N = 13$), and the upper boundary of the 95% CI (35.3%) was lower than the targeted stabilisation rate of 40%.

Overall, 17 patients reached CR or PR: 10 in arm A and 7 in arm B. Median (range) time from randomisation to CR/PR was 8 weeks (7–11 weeks) in arm A and 14 weeks (5–16 weeks) in arm B. All 17 CR/PR patients relapsed. Median (range) DFS was 8.1 months (3.2–18.9 months) in arm A and 7.4 months (5.6–10.8 months) in arm B.

Fig. 1 shows that the median PFS estimates in arms A and B were 4.3 months (95% CI 2.2–6.1) and 1.5 months (95% CI 1.4–1.9), respectively, and the estimated 1-year PFS rates were 11.1% (SE = 4.7%) and 2.3% (SE = 2.2%), respectively. Fig. 2 indicates that the median OS estimates in arms A and B were 9.5 months (95% CI 6.9–13.7) and 10.5 months (95% CI 7.5–13.0), respectively, and the estimated 1-year rates were 37.8% (SE = 7.2%) and 46.7% (SE = 7.6%).

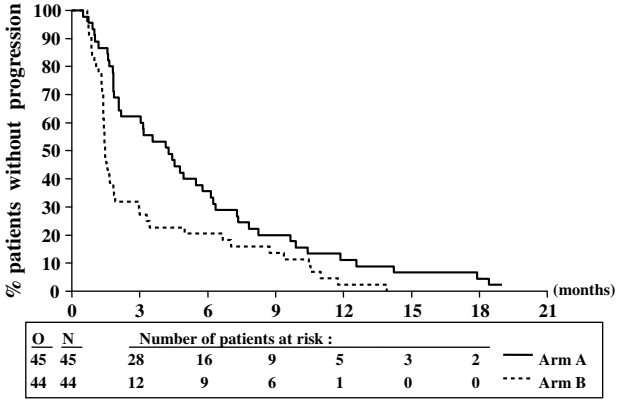

Fig. 1 – Progression-free survival.

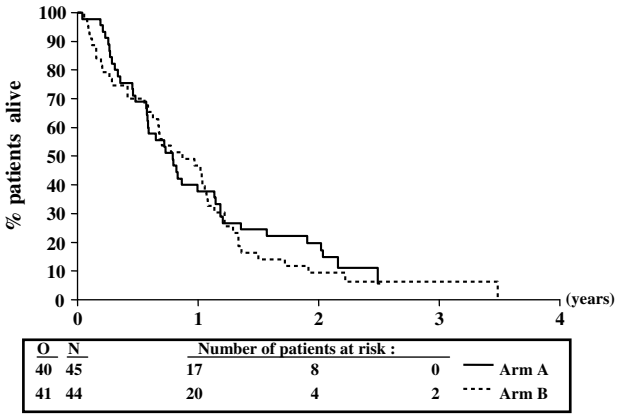

Fig. 2 – Overall survival.

5. Discussion

In this study, we investigated whether two cycles of dacarbazine monotherapy could select for the subgroup of patients with metastatic melanoma that would benefit most from more intensive chemoimmunotherapy. As expected, toxicity was much lower for the first two cycles with dacarbazine compared with the 4-drug chemoimmunotherapy regimen.

Pretreatment with two cycles of dacarbazine monotherapy prior to a 4-drug chemoimmunotherapy regimen resulted in a stabilisation rate lower than the pre-set target of 40%. In contrast, those who received the 4-drug chemoimmunotherapy regimen from the beginning had a stabilisation rate of 42.2%, which is consistent with the pre-set target. Therefore, we conclude that initial treatment with two cycles of dacarbazine is not an appropriate method to select for patients who may benefit from more intensive chemoimmunotherapy. The fact that responses on chemoimmunotherapy were rare in patients with PD after dacarbazine monotherapy indicates the existence of at least partial cross resistance between these regimens. Results on response, progression-free survival and overall survival in arm A were comparable to the results of the same 4-drug chemoimmunotherapy which we have applied in our previous phase III study.[2] Despite a lower stabilisation rate and a shorter PFS observed in arm B than in arm A, OS of the two treatment groups were comparable. Probably, this is due to the fact that the response rates were low and the responses were of short duration, as indicated by the median DFS of 8.1 and 7.4 months in arms A and B, respectively.

After the accrual of this study had been completed, the results from randomised phase III studies have shown that chemoimmunotherapy does not provide any clinical benefits for patients with metastatic melanoma over chemotherapy alone.[7–12] Furthermore, our previous study has demonstrated that the addition of IL-2 to a regimen of dacarbazine, cisplatin and IFN-α also does not result in a survival benefit.[2]

To date, no treatment has shown any benefit in terms of efficacy or toxicity over treatment with dacarbazine alone.

Currently, our group is conducting a phase III randomised trial 18,032 comparing dacarbazine to an intensified regimen of temozolomide. There is a great need for novel drugs with higher efficacy in melanoma.

Conflict of interest statement

Dr. C.J.A. Punt is on advisory boards and has received honoraria of Roche, Pfizer, Sanofi-Aventis and AstraZeneca.

Dr. U. Keilholz has received honoraria from Chiron and ScheringPlough: less than $10.000 and research funding from Chiron: less than $100.000. No stock ownership and others.

Dr. M. Gore has received honoraria for advisory boards and lectures from ScheringPlough.

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