Long-term Survival of Stage IV Melanoma Patients Treated with BOLD Combination Chemotherapy and Intermediate-dose Subcutaneous Interferon-alpha

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Abstract. *Background: Immune checkpoint and serine/threonine-protein kinase inhibitors have become a standard of care for advanced cutaneous melanoma, but dacarbazine-based chemotherapies are occasionally used. This study assessed the long-term efficacy of chemoimmunotherapy (bleomycin, vincristine, lomustine and dacarbazine with/without subcutaneous interferon-alpha: BOLD-INF- α) as real-world data in patients with metastatic melanoma not eligible for clinical trials. Patients and Methods: Medical data of 146 patients with stage IV melanoma who had received BOLD/BOLD-INF α regimen during 1991-2010 were analyzed. Results: The median overall survival was 8.9 months (95% confidence interval=7.5-10.4 months). The 1-year survival rate was 36%, 2-year 18%, and 5-year 13%. The 5-year survival rates in the M1a, M1b and M1c subgroups were 28%, 10% and 6%, respectively. Overall, 7% (n=11) of the patients were alive at the end of the follow-up. Conclusion: Our study showed similar overall survival among patients with stage IV cutaneous melanoma treated with BOLD/BOLD-INF α as noted previously with chemotherapy.*

The treatment of advanced melanoma is evolving rapidly. Dacarbazine or temozolomide were the standard of treatment before the development of immune checkpoint inhibitors, anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) agent ipilimumab (1, 2) and anti-programmed cell death protein 1 (PD1) agent nivolumab (2, 3) and pembrolizumab (2, 4), as well as the v-Raf murine sarcoma viral oncogene

homolog B (BRAF) inhibitors vemurafenib (2, 5), dabrafenib (2, 6) and trametinib (6). Single-agent dacarbazine was associated with an objective response rate (ORR) of 13% and the median overall survival (OS) of 8.9 months (range=5.6-11 months) (6). A previous meta-analysis showed that combination of dacarbazine with older immunotherapies, *i.e.* interferon-alpha (INF α) or interleukins, increased ORR to 21.5% (7). Combination chemotherapy with bleomycin, vincristine, lomustine and dacarbazine (BOLD) and INF α increased the ORR even up to 62% with 13% complete responses (CR) and 49% partial responses (PR), as reported in a phase II clinical trial (8). Another phase II clinical trial showed six CRs among patients with stage 4 melanoma with soft-tissue and lung metastases treated with BOLD-INF α (9).

Although BOLD-INF α was shown to lead to a higher ORR compared to single-agent dacarbazine, it failed to prolong OS (9-12). In a Finnish four-armed, randomized, phase II clinical trial, single-agent dacarbazine, or BOLD were combined with natural or recombinant INF α in the treatment of patients with advanced cutaneous melanoma. Tumor responses tended to be higher with BOLD combined with recombinant INF α , but there was no significant difference in OS between the different treatment arms. The median OS in that study was 9.0 months and 7% of the patients survived over 5 years (9). Other combination chemotherapy regimens such as cisplatin with vinblastine and dacarbazine (CVD), Dartmouth Regimen (dacarbazine, carmustine, cisplatin, tamoxifen) and carboplatin with paclitaxel have also been used in the treatment of advanced melanoma, with similar OS results (6, 10, 12).

The 5-year survival rate among patients with stage 4 melanoma treated with dacarbazine is low, ranging from 6-9% (10, 13). In a recent analysis of treatment-naïve patients with advanced melanoma who had received ipilimumab plus dacarbazine or dacarbazine alone, the survival rate of the dacarbazine-treated arm was 36% at 1 year, 18% at 2 years, 12% at 3 years and 9% at 5 years (13). A 5-year survival rate of 10% was also recorded in patients

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with metastatic melanoma treated with BOLD-INF α chemoimmunotherapy (14). The aim of our study was to analyze the long-term survival of patients with stage IV cutaneous or unknown primary melanoma treated with BOLD/BOLD-INF α in a retrospective real-world evidence patient population treated outside clinical trials before acceptance of modern therapies and to analyze prognostic factors for survival.

Patients and Methods

Patients. The study population consisted of patients with metastatic cutaneous or unknown primary melanoma considered eligible for combination chemotherapy at the Department of Oncology and Radiotherapy at Turku University Hospital, Finland, during 1991-2010. Patients were not eligible for surgery or radiotherapy alone, nor for any clinical trial. All patients received at least one cycle of BOLD with or without subcutaneous INF α during the course of their disease. This time period was selected because new immunotherapies or BRAF inhibitors were not available outside clinical trials until 2010. Patients were followed-up until March 30th, 2016. The median duration of follow-up was 8.9 months (range=0.8-224.5 months).

During 1991-2010, altogether 153 patients received BOLD/BOLD-INF α for the treatment of stage IV melanoma. Five patients were excluded due to missing follow-up data and one patient with uveal and one patient with gastrointestinal primary melanoma were excluded. Thus, a total of 146 patients were included in this analysis. The study cohort represented a real-life patient population with stage IV melanoma eligible for chemotherapy attending our clinic.

Study design. This study was a retrospective cohort study. Survival data were obtained from Statistics Finland. Medical histories of study patients were gathered from Turku University Hospital patient records. The primary objective of our study was to assess the long-term survival of patients with stage IV melanoma treated with BOLD/BOLD-INF α before modern therapies were available. Secondary objectives were to analyze progression-free survival (PFS), ORR, safety of BOLD/BOLD-INF α regimens and prognostic factors for survival.

Treatment. The BOLD-INF α regimen comprised 15 mg bleomycin intravenously (*i.v.*) on days 2 and 5, 1 mg/m² vincristine *i.v.* to a maximum of 2 mg on days 1 and 4, 80 mg lomustine orally on day 1 and 200 mg/m² dacarbazine *i.v.* on days 1-5. One cycle lasted for 28 days. INF α was administered subcutaneously at 3 MIU daily starting on day 8 for 6 weeks and 6 MIU three times per week thereafter. The treatment was continued until unacceptable toxicity, deterioration of patient's performance status or disease progression (PD) (15).

Statistical analysis. Statistical analyses were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY, USA). Effect measures are presented with 95% confidence intervals (CI). Kaplan-Meier curves were prepared to analyze the OS and the PFS. Differences in OS between the subgroups were analyzed pairwise. OS was calculated from the beginning of the BOLD/BOLD-INF α treatment to death or the last day of follow-up. PFS was calculated from the beginning of the BOLD/BOLD-INF α treatment to computed tomographic scan-detected disease progression or to the beginning of best supportive care. Investigator-assessed RECIST 1.1. criteria (15) were used for

the treatment response analysis. The Cox regression method was used to analyze the association of prognostic factors with death.

Results

Patients and treatment. A total of 146 patients received at least one dose of BOLD/BOLD-INF α . The median number of BOLD/BOLD-INF α cycles was 4 (range=1-13); 62% (n=91) received 1-4 cycles and 38% (n=55) 5-13 cycles of BOLD/BOLD-INF α . Ninety-two percent (n=134) of the patients received BOLD with subcutaneous INF α , and only 8% (n=12) received BOLD alone. Receipt of oncological therapy before and after BOLD/BOLD-INF α varied markedly. Adjuvant INF α (n=12, 8%), dacarbazine-INF α (n=3, 2%) and isolated limb perfusion (n=3, 2%) were the most common therapies before BOLD/BOLD-INF α . Cisplatin-etoposide or carboplatin-etoposide (n=28, 19%), alkylating chemo-therapeutic agents (temozolomide, dacarbazine or BOLD re-challenge) (n=26, 18%) and subcutaneous INF α maintenance therapy (n=24, 16%) were the most common subsequent therapies. Fifty-seven percent (n=83) of the patients had received radiotherapy and 56% (n=82) had undergone operative treatment of metastases. Characteristics of the study population are summarized in Table I.

Efficacy and safety. The median PFS of patients treated with BOLD/BOLD-INF α therapy was 3.8 months (95% CI=3.0-4.6 months). The investigator-assessed ORR was 29% (n=43). Partial response (PR) was achieved in 23% (n=33) and complete response (CR) in 7% (n=10) of the patients, while 24% (n=35) of the patients achieved stable disease (SD); PD was found in 46% (n=68) of the patients. The most common causes for the termination of BOLD/BOLD-INF α therapy were PD in 61% (n=89) of the patients, adverse events (AE) in 12% (n=18) of the patients, and planned termination after six or eight cycles of BOLD in 12% (n=18) of the patients. The most common AEs were fatigue in 38% (n=56), hematological (anemia, neutropenia, thrombo-cytopenia) in 23% (n=34) and peripheral neuropathy in 23% (n=34). There were 15 cases of pulmonary reactions probably related to bleomycin. The incidence of AEs may have been underestimated because of the lack of systematic reporting of AEs outside of clinical trials.

Overall survival. A total of 135 deaths had occurred by the end of the follow-up. Two causes of deaths were not melanoma related, one being heart failure and the other being hemorrhagic gastritis. The median OS was 8.9 months (95% CI=7.5-10.4 months). The 1-, 2- and 5-year survival rates were 36% (n=53), 18% (n=27) and 13% (n=19), respectively. Seven percent (n=11) of the patients were alive at the end of the follow-up. The characteristics of 5-year survivors are summarized in Table II.

The M-stage according to American Joint Committee on Cancer 7th edition (16) was significantly associated with OSI

Table I. Characteristics of 146 patients with stage IV melanoma.

Characteristic	Value
Age, years	
Median (range)	58 (21-79)
Male	97 (66%)
Female	49 (34%)
Charlson comorbidity index	
Median (range)	6 (6-12)
ECOG PS	
0	22 (15%)
1	82 (56%)
2-3	19 (13%)
Unknown	23 (16%)
Primary melanoma	
Cutaneous	128 (88%)
Unknown	18 (12%)
M-Stage*	
M1a	39 (27%)
M1b	39 (27%)
M1c	68 (46%)
Treatment	
BOLD–INFα	134 (92%)
BOLD	12 (8%)
Number of cycles of BOLD/BOLD–INFα	
Median (range)	4 (1-13)
Oncological therapy before BOLD/BOLD–INFα	
Yes	24 (16%)
No	122 (84%)
Oncological therapy after BOLD/BOLD–INFα	
Yes	71 (49%)
No	72 (49%)
Unknown	3 (2%)
Radiotherapy of metastases	
Yes	83 (57%)
No	62 (42%)
Unknown	1 (1%)
Surgery of metastases	
Yes	82 (56%)
No	64 (44%)

ECOG PS: Eastern Cooperative Oncology Group performance status; BOLD: bleomycin, vincristine, lomustine and dacarbazine; INFα: interferon-alpha; M-stage: metastasis stage. *According to American Joint Committee on Cancer 7th edition (16).

($p=0.001$) in the Kaplan–Meier (log-rank) analysis. In pairwise comparisons, the survival of the M1a was significantly better than that of the M1c subgroup ($p<0.001$) as was that of the M1b subgroup ($p=0.041$). The survival rates are presented in Table III.

Prognostic factors. A Cox regression analysis was performed to analyze the prognostic factors of death in the study cohort. Variables in the analysis consisted of gender (male/female), site of primary melanoma (cutaneous/unknown primary), age at the beginning of BOLD/BOLD–INFα (years), Charlson comorbidity index (17), Eastern Cooperative Oncology

Table II. Characteristics of 19 patients with stage IV melanoma surviving 5 years.

Characteristic	Value
Age, years	
Median (range)	59 (40-79)
Gender, n (%)	
Male	7 (37%)
Female	12 (63%)
ECOG PS, n (%)	
0	7 (37%)
1	10 (53%)
Unknown	2 (10%)
M-Stage, n (%)	
M1a	11 (58%)
M1b	4 (21%)
M1c	4 (21%)
Number of cycles BOLD/BOLD–INFα, n (%)	
Median (range)	5 (1-10)
Oncological therapy before BOLD/BOLD–INFα, n (%)	
Yes	5 (26%)
No	14 (74%)
Oncological therapy after BOLD/BOLD–INFα, n (%)	
Yes	11 (58%)
No	8 (42%)
Surgical therapy of metastases, n (%)	
Yes	16 (84%)
No	3 (16%)
Radiotherapy of metastases, n (%)	
Yes	12 (63%)
No	7 (37%)

ECOG PS: Eastern Cooperative Oncology Group performance status; BOLD: bleomycin, vincristine, lomustine and dacarbazine; INFα: interferon-alpha; M-stage: metastasis stage. *According to American Joint Committee on Cancer 7th edition (16).

Group (ECOG) performance status (0/1/2/3), M-stage (M1a/M1b/M1c), regimen (BOLD/BOLD–INFα), number of BOLD/BOLD–INFα cycles ($n=1-4/n=5-13$), radiotherapy of metastases (yes/no), surgical therapy of metastases (yes/no), oncologic therapy before BOLD/BOLD–INFα (yes/no) and oncologic therapy after BOLD/BOLD–INFα (yes/no).

Fewer BOLD/BOLD–INFα cycles ($p<0.001$), poorer baseline ECOG performance status ($p=0.001$), male gender ($p=0.001$), absence of chemotherapy after BOLD/BOLD–INFα ($p=0.006$) and more advanced M-stage ($p=0.012$) were adverse prognostic factors in the multivariate analysis. The hazard ratio (HR) of death was 3.4 (95% CI=2.1-5.4) among patients who had received 1-4 BOLD/BOLD–INFα cycles compared to those who had received 5-13 BOLD/BOLD–INFα cycles. The HR of death was 1.9 (95% CI=1.3-2.8) following each decline in baseline ECOG performance status. The HR for death of men was 2.1 (95% CI=1.3-3.4) compared to women. The HR of death was 1.9 (95% CI=1.2-3.0) for those who did not receive chemotherapy after BOLD/BOLD–INFα and 1.4 (95% CI=1.1-1.9) for each advance in M-stage.

Table III. *Survival rates and median overall survival (OS) of study patients according to M-stage (16).*

Subgroup	Survival rate			Median OS (95% CI), months
	1-Year	2-Year	5-Year	
M1a (n=39)	51%	38%	28%	12.7 (8.7-16.6)
M1b (n=39)	38%	13%	10%	10.3 (7.9-12.6)
M1c (n=68)	26%	10%	6%	6.4 (4.7-8.2)
Total (n=146)	36%	18%	13%	8.9 (7.5-10.4)

CI: Confidence interval.

Discussion

Our retrospective study demonstrated similar efficacy and long-term survival rate with BOLD/BOLD- $\text{INF}\alpha$ in patients with stage IV melanoma treated outside clinical trials, as noted in previous clinical trials with dacarbazine-based chemotherapy (2, 9, 12, 13). The 5-year survival rate of 13% in this cohort was relatively high and 7% of patients were still alive at the end of the follow-up, representing long-term survivors. Treatment was feasible and was discontinued in only 12% because of AEs. At 29%, the ORR with BOLD/BOLD- $\text{INF}\alpha$ was higher than that achieved with single-agent dacarbazine with/without $\text{INF}\alpha$ in clinical trials (6, 7).

We analyzed clinical factors which might be associated with better survival. Fewer BOLD/BOLD- $\text{INF}\alpha$ cycles was associated with shorter survival. The number of BOLD/BOLD- $\text{INF}\alpha$ cycles was also correlated to the response to therapy. The first response evaluation with computed tomographic scan was usually taken after three cycles of BOLD/BOLD- $\text{INF}\alpha$ and patients with PD were subjected to another therapy or palliative care. Subsequent therapies were associated with better survival, which is probably related to the effect of these therapies on survival and the ability to give subsequent therapies to patients with favorable response to BOLD/BOLD- $\text{INF}\alpha$. AJCC M-stage was associated with better survival in the Kaplan-Meier analysis and in the multivariate analysis. For the M1a subgroup, the plateau in the survival curve was reached at a survival rate of 18%. Lower tumor burden and better performance status have also been suggested to predict better prognosis with immunotherapies (2).

Limitations of this study include its retrospective design, lack of a control group and a small number of patients. During 1991-2010, BOLD/BOLD- $\text{INF}\alpha$ was the standard first-line treatment option for stage IV melanoma at our clinic and our study cohort represents a typical real-life population of patients with stage IV melanoma eligible for chemotherapy. Our findings were consistent in terms of OS and long-term survival with earlier studies of BOLD- $\text{INF}\alpha$ chemoimmunotherapy (8, 9, 14).

Immune checkpoint inhibitors and BRAF and mitogen-activated protein kinase (MEK) inhibitors have replaced chemotherapy in the first-line therapy option for stage IV melanoma (2). A pooled analysis of the long-term OS data from phase II and III clinical trials with ipilimumab in advanced melanoma showed a median OS of 11.4 months and 3-year median OS of 22% (18). The median OS of stage IV melanoma is being further extended in current clinical trials with anti-PD1 agents nivolumab and pembrolizumab (19, 20), combination immunotherapy with anti-CTLA4 agent ipilimumab plus nivolumab (21), as well as with the combination of BRAF and MEK inhibitors vemurafenib and cobimetinib (22), and dabrafenib and trametinib (23, 24). Unfortunately, the majority of patients still develop PD during novel therapies and subsequent treatment options are needed. In addition, patients with wild-type *BRAF* gene and poor performance status (>1), high serum lactate dehydrogenase (more than twice normal upper level), or with symptomatic brain metastases have only very limited treatment options. We conclude that traditional dacarbazine-based chemoimmunotherapy may still be a feasible treatment option for patients with stage IV melanoma not suitable for modern therapies.

Conflicts of Interest

The Authors declare that there is no conflict of interests in regard to this study.

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