High-dose Interleukin-2 and Interferon as first-line immunotherapy in metastatic melanoma. Long-term follow-up in a large unselected Danish patient cohort

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Abstract:

Background and patients
Between January 2007 and April 2014, 464 Danish patients received high-dose (HD) Interleukin-2 (IL-2) and Interferon(IFN) as first-line treatment for metastatic melanoma. Our data represents the largest cohort of metastatic melanoma patients world-wide, with relevant data on all patients and no patients lost to follow-up. Data has been gathered in a national database on the treatment of metastatic melanoma established since 2011.

Results
118 patients (25%) obtained an objective response (ORR) to treatment with a median progression free survival (PFS) of 3.4 months and a median overall survival (OS) of 14.2 months. Further, 2, 3 and 5-year survival was 32.0%, 23.2% and 16.6%, respectively. Ipilimumab as second-line therapy has been used since July 2010. We divided patients in two subgroups before and after this date to evaluate the effects of new treatment strategies. Patient characteristics, ORR and PFS were comparable in the two subgroups. Survival was significantly improved after 2010, with an increase in median OS from 12.2 to 16.0 months and in 5-year OS from 12.5% to 20.7%.

Conclusions
Our data confirms that HD IL-2/IFN as first-line therapy in metastatic melanoma leads to long term survival in a subset of treated patients. Potentially IL-2/IFN might represent a treatment option in patients with active melanoma after established initial treatment with checkpoint inhibitors and BRAF/MEK targeted therapies.

Keywords:
Interleukin-2; Interferon; metastatic melanoma; immunotherapy; long-term survival
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Introduction

Interleukin-2 (IL-2) represents the first successful immunotherapeutic intervention in clinical oncology, approved by FDA for treatment of metastatic melanoma in 1998. This was a major breakthrough, since it was the first time that modulation of the immune system turned out to be an effective therapy for cancer. In March 2011, ipilimumab targeting CTLA-4 was approved by the FDA. Since then, a further two checkpoint inhibitors targeting PD-1 have been approved (nivolumab and pembrolizumab (2014)). With the increasing use of combination immunotherapy targeting both CTLA-4 and PD-1, patients with BRAF wildtype (wt) metastatic melanoma may have an unmet need for further immunotherapy if failing on combination immunotherapy. IL-2 based immunotherapy may be a treatment option in these patients. We present national “real-world” data from a large unselected patient population receiving IL-2 and IFN as first-line treatment between January 2007 and April 2014.

Material and Methods

Based on our prior experience with IL-2 based therapy [1], we achieved national approval in 2008 to change the standard of care in Danish metastatic melanoma patients to a regimen with high-dose (HD) IL-2 and interferon-alpha 2b (IFN) given intravenously in combination [2].

We developed specialized units within the Departments of Oncology at Odense University Hospital, Aarhus University Hospital (2008) and Copenhagen University Hospital, Herlev (2010) in order to standardize treatment for Danish patients with metastatic melanoma. All Danish patients with metastatic melanoma were referred to one of the three centers. Each center followed a standard protocol of baseline evaluation for selection of patients eligible for HD IL-2/IFN therapy, treatment administration and follow-up, with evaluation at specified time points.

Baseline staging included patient history; physical examination, including ECOG performance status (PS); imaging (CT of the brain, neck, chest and abdomen); and, blood chemistry (hemoglobin, WBC, granulocyte counts, platelet counts, CRP, sodium, potassium, creatinine, ALAT, LDH, alkaline phosphatases). Patients with brain metastases were offered treatment if they were asymptomatic and had a limited number of metastatic lesions located in areas of the brain where the estimated risk of treatment induced edema would not be life threatening. Based on Danish data [1], later confirmed in a larger EORTC dataset [3], we did not offer HD IL-2 based treatments to patients with high WBC, high LDH combined with an ECOG performance status of 2 or more.

IL-2/IFN was administered according to a regimen developed by Keilholz et al. [4]. Until July 2009, IFN dose was given as interferon alpha 2b (IntronA, Schering Plough), 10 MU sc, on days 1, 3 and 5. Thereafter, IFN was given as pegylated interferon alpha-2b, (Peg-Intron, Schering Plough), 300 mikrogr sc, on day 1. The HD IL-2 regimen started in week 2 and consisted of aldesleukin (Proleukin, Novartis) 18 MU/m² in the first 6 hours, 18 MU/m² in the next 12 hours, 18 MU/m² in subsequent 24 hours, and followed by 4.5 MU/m² per day for the next 3 days. IL-2 was administered as continuous iv. infusions.

We retrospectively collected and gathered data in a national database which includes treatment details on Danish patients with metastatic melanoma. The database was established in 2011, including data on baseline characteristics, key biomarkers, given treatment and efficacy parameters. No data on toxicity was collected. Patient and disease characteristics were analyzed using descriptive statistics and expressed as relative frequency (percentage) for discrete variables or medians for continuous variables.
Response to treatment was evaluated using RECIST 1.0 [5], based on CT-imaging. CT was performed at baseline and repeated after 2 courses of HD IL-2/IFN. Patients responding to treatment (PR or CR) were offered 2 or 4 additional treatment courses. Patients with stable disease (SD) were offered 2 additional courses, except in cases where a marked imbalance between risk for toxicity and chance of efficacy was evident. Patients with PD after 2 courses stopped treatment. Patients in post treatment follow-up had a repeated CT-scan every 3 months for 2 years after treatment start and, thereafter, at 6 months intervals until 5 years. Follow-up for survival continued past this point, with repeat CT-scans only on indication.

PFS and OS were evaluated using Kaplan–Meier analyses and expressed as medians, and as 2, 3 and 5 year survival. Differences between curves were evaluated using the log-rank test.

Evaluation of OS related to the following known prognostic markers using univariate log-rank test was performed: gender, age (cutpoint: median age), primary melanoma site (cutaneous vs unknown primary), LDH (<ULN vs 1-2 x ULN vs >2 x ULN), WBC (<= ULN vs > ULN), granulocyte count (<= ULN vs > ULN), and M-stage (M1c vs M1a, M1c vs M1b).

With the availability of ipilimumab in July 2010 and later also approval of drugs targeting BRAF mutations, relevant second-line treatment option after IL-2 became available. To test the hypothesis of positive impact of these new treatment options, we divided our material in two subgroups, before and after 1 July 2010. We compared the above mentioned biomarkers in the two groups and subsequent analyses of RR, PFS and OS were performed.

Results

Between January 2007 and April 2014, 464 patients with metastatic melanoma initiated treatment with first-line HD IL-2/IFN. No patients were lost to follow-up. Final evaluation of included patients was performed as of 31 December 2017. Baseline characteristics are presented in table 1. The median age was 59 years with no change in median age over the time period of 7 years. The majority (62.3%) had M1c disease. 18 patients (3.9%) had brain metastases and 43.5% had elevated LDH at baseline.

At the time of analysis, median Kaplan-Meier estimated follow-up time was 77.1 months (6.4 years), with the last patient receiving the first dose of HD IL-2/IFN on 1 April 2014. No treatment related deaths was observed during the treatment period.

Among 464 patients, 461 were evaluated for response according to RECIST (Table 2). 118 patients obtained a response leading to an objective response rate (ORR) of 25.3%. 44 of these patients (9.4%) obtained a CR and 74 obtained a PR (15.9%).

Median PFS was 3.4 months with 8.0%, 7.1% and 6.0% maintaining response after 2, 3 and 5 years, respectively (Fig. 1). The median duration of CRs was 65.9 months. For patients obtaining PR or stable disease (SD), the median duration was 7.4 and 4.2 months, respectively.

Median overall survival (OS) was 14.2 months, with 32.0%, 23.2% and 16.6% being alive after 2, 3 and 5 years, respectively (Fig. 1). The median OS of patients obtaining a CR was not reached. Further, for patients obtaining PR or stable disease (SD), the median OS was 20.4 and 16.3 months, respectively.

Age, gender and known vs unknown primary melanoma did not impact OS (Table 3). Evaluation of OS according to M-stage revealed that both M1a and M1b have a significantly longer OS than M1c patients.
Evaluating baseline biomarkers revealed that LDH (normal vs 1-2 x ULN, >2 x ULN), ECOG PS (0 vs 1 vs 2), white blood cell count (WBC) (normal vs > ULN), and granulocyte counts (normal vs > ULN) had a significant influence on OS (Table 3).

In the two subgroups before \( n=232 \) and after \( n=232 \) July 2010, we checked for differences in baseline clinical characteristics, finding no statistically significant difference between the two subgroups except for performance status. The cohort treated before 1 July 2010 had a slightly poorer ECOG performance status (supplementary Table S1).

Analysis of the two groups revealed that in the early patient-cohort, 131 patients (56.9%) did not receive any further antineoplastic therapy after first-line IL-2 and IFN. This number was reduced to 68 (29.3%) in the 2\textsuperscript{nd} period. Details on subsequent treatments are presented in supplementary Table S2.

All PFS results at 2, 3 and 5 years were exactly identical before and after 1 July 2010 (Table 4). Median OS was increased from 12.2 to 16.0 months, with a subsequent improvement also in 5 year OS from 12.5% to 20.7%. In univariate analysis, this difference was significant with a hazard rate (HR) of 1.37, \( p=0.002 \).

Discussion

We present retrospectively collected real life data on an unselected patient cohort with metastatic melanoma treated with HD IL-2/IFN as first line treatment in Denmark over a 7 year period. Denmark covers a population of approx. 5.5 million people. All patients received treatment according to nationally standardized guidelines.

FDA approval of HD IL-2 for the treatment of metastatic melanoma in 1998 led to a large number of clinical trials evaluating different IL-2-based treatment regimens. Several questions were addressed in these trials, but only a few firm conclusions were drawn. Atkins et al. [6] emphasized the importance of obtaining a CR in order to significantly impact survival. A high CRR can be obtained by using an HD IL-2 regimen. The biochemotherapy combination of IL-2 and cytotoxic chemotherapy (BCT) leads to an increase in PRR only, offering a possible explanation as to why the higher RR obtained with BCT did not lead to survival improvement. This was confirmed by Atkins et al., showing that 60% of the CRs were long lasting and that these patients potentially had been cured for metastatic disease [7]. The median duration of CR in our study was 65.9 months. The potential of IL-2 to induce long lasting responses was also confirmed by Richards et al. [8] and Keilholz et al. [9].

The HD IL-2 regimen induces significant toxicity, and the strategy of centralizing treatment is therefore important in order to secure optimal toxicity management. Probably this also explains why we observed no treatment related deaths. In a US cross-sectional study, Mehta et al. [10] showed a significant decline in treatment related mortality of renal cell cancer and metastatic melanoma patients treated with HD IL-2 with increasing number of patients treated, emphasizing the importance of experienced and skilled staff taking care of these patients.

OS is the ultimate endpoint. However, with the increase in available treatment options, subsequent treatments may influence survival, and this calls for the use of other endpoints such as PFS and RR. In our study, we found an ORR, CRR and PRR of 25.3%, 9.4% and 15.9%, respectively. Atkins et al. [6, 7] reported ORR, CRR and PRR of 16%, 6% and 10%, while Keilholz et al. [11] reported 18%, 6% and 12%. The corresponding figures in the meta-analysis by Bright et al. [12] were 19.7%, 4.8% and 12.5%, respectively. In
the paper by Atkins et al. [6], only 54% of the patients received IL-2 as first-line treatment, while the corresponding figure from Keilholz et al. [11] was 78%. This may explain the difference in response rates as all of our patients were treated in first-line. The increase in clinical experience gained over the years may also have resulted in a higher dose intensity of IL-2 offered to our patient population, compared to the published data collected from multiple institutions. One study by Dorval et al [13] evaluated IL-2/Cisplatinum +/- IFN with a limited number of patients (n=117) revealing a non-significant increase in response rate, but no difference in OS. Therefore, the addition of IFN in our schedule may also have contributed to the higher response rates we found.

In our analysis, median OS was 14.2 months. In general, a tendency for “the tail of the survival curve” to become horizontal in patients receiving immunotherapy when having passed 3 years has been established in modern immunotherapy trials, indicating no further melanoma related events. This has changed the focus from median survival to long term survival rates instead. We found survival rates at 2, 3 and 5 years of 32.0%, 23.2% and 16.6%, respectively. Further, this compares favorably with data from Keilholz et al. [14], reporting a 2-year survival of 23% and a 5-year survival of 13%. Payne et al. [15] reported a single-institution experience in renal cell carcinoma and melanoma using IL-2, and in the subset of 314 melanoma patients, they found a 2-year survival of 41% and a 5-year survival of 23%.

We divided the patient material into two subgroups before and after ipilimumab as second-line treatment became available. Using PFS as endpoint, we found overlapping survival curves. Combined with unchanged ORR, this indicates that the efficacy of the HD IL-2/IFN regimen did not change over time.

The analysis of the two subgroups with OS as endpoint reveals a significant increase. This may reflect the impact of subsequent medical therapies in 2nd and later lines. Median OS increased from 12.2 months to 16.0 months. Looking at the patients treated before July 2010, where the use of check-point inhibitors in second-line was scarce, 12.5% of patients were alive after 5 years, demonstrating that long lasting responses can be induced with HD IL-2/IFN. Turning to the group of patients treated after July 2010, the 5-year survival increased to 20.7%. This is accordance with retrospective data from Joseph et al [16] finding 17% of patients who did not require further systemic therapy after treatment with IL-2. Further 7 patients out of 48 patients receiving Ipilimumab after progressing on IL-2 were alive after 2 years.

This shows that subsequent treatment with check-point inhibitors and/or BRAF/MEK targeting agents after PD on HD IL-2 treatment may induce new responses and prolong OS. However, there is no indication of an additive effect of ipilimumab administered after HD IL-2 in our data, comparing with published data on long term efficacy of ipilimumab. [17]

With respect to sequencing of HD-IL2 and ipilimumab, a randomized trial has been conducted by Patel et al according to ClinicalTrials.gov (NCT01856023). No published data is available. Buchbinder et al. [18] published retrospective data on the use of second-line HD IL-2 in patients progressing on ipilimumab. An ORR of 21% was obtained in the prior ipilimumab arm compared to 12% in the group with no prior ipilimumab. They concluded that HD IL-2 was active in patients with progression following ipilimumab and that toxicity was not worsened.

A recent publication from the same researchers [19] have confirmed that HD-IL2 have efficacy also after progression on drugs targeting PD-1/PD-L1, revealing efficacy data comparable to the data we present here with IL-2/IFN as first line therapy.
We conclude that IL-2/IFN as an immune system stimulator combination used as first line systemic treatment for metastatic melanoma, can lead to complete and durable response in a small subset of patients. Our data cannot directly support the use of this treatment option after progression on modern immunotherapy and targeted therapies. However, in patients with no treatment options, HD IL2/IFN may be a treatment option to be considered. The efficacy data presented combined with the well described significant toxicities of HD-IL-2 based regimens cannot justify a randomized trial evaluating HD IL-2/IFN against modern checkpoint inhibitors. It is also important to note, that HD IL-2 should only be used in specialized centers and this might influence the decision on whether or not to use this treatment option. Whether or not to use this treatment combination or perhaps including pegylated IL-2 (NKTR-214)[20] can only be definitively evaluated in a prospective clinical trial.
References


