Combining surgery and systemic therapy in metastatic melanoma

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PART II

Adjuvant immunotherapy

Chapter 4

Adjuvant systemic therapy in high-risk melanoma

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Melanoma Res. 2019 Aug;29(4):358-364

ABSTRACT

In resected high-risk melanoma (stage IIB/C-III) the risk of locoregional and/or distant recurrence is substantial and so far adjuvant therapies have been fairly unsuccessful. Interferon showed slight improvements in recurrence-free survival (RFS), but failed to convincingly improve overall survival (OS). In these patients adjuvant therapy with treatments that show promising results in stage IV disease is arising.

Studies using immune checkpoint blockade with anti-CTLA-4 and anti-PD-1 agents reveal convincing RFS benefits. OS rates, however, are not mature yet in most studies. Only ipilimumab has shown an OS benefit but at a high cost of toxicity. Also in studies with adjuvant targeted therapy using BRAF and MEK inhibitors, ensuring results are reported regarding RFS. As possible toxicity cannot be ignored, it is crucial to identify patients who would benefit most from these adjuvant therapies.

In patients with clinically detectable lymph node metastases, studies using neoadjuvant schedules of immunotherapy and targeted therapy have been performed. In phase I and II studies the most optimal schedule of combination immunotherapy was identified and further research on this front will follow in the coming years.

Concluding, after decades of scarce options for patients with high-risk melanoma, recent developments in adjuvant therapy have changed the standard of care for these patients.

INTRODUCTION

The incidence of cutaneous melanoma has been increasing over the past decades. The WHO estimates there will be about 287 000 new cases of melanoma worldwide in 2018, causing over 60 700 deaths this year.[1] Predictive factors associated with survival are Breslow thickness, ulceration, number of positive lymph nodes, tumor burden, distant metastasis and serum lactate dehydrogenase level.[2, 3]

Surgery is the cornerstone in the treatment of melanoma in stage I, II, and III. For localized disease, the standard of care is wide local excision of the primary tumor, with additional safety margins dependent on the Breslow thickness. In addition, sentinel node (SN) biopsy is recommended by most guidelines, to provide information on the lymph node status, for primary melanomas with a Breslow thickness of over 1.0 mm, or less than 1.0 mm with multiple additional risk factors. As both the MSLT-II and DECOG-SLT study showed no survival benefit of CLND compared with the nodal observation by ultrasound, completion lymph node dissection (CLND) in case of a positive SN has become obsolete.[4, 5] Therefore, lymph node dissections are now only reserved for clinically detectable lymph node metastasis by most guidelines.

Despite multiple efforts to improve surgical options and to maintain locoregional control, there is a substantial risk of locoregional and/or distant recurrence in resected high-risk melanoma (stage IIB/C – III) because of the presence of undetectable hematogenous micrometastases already at the time of diagnosis. Together with this risk of recurrence, mortality rates increase with increasing tumor stage. Survival rates for stage III according to the AJCC 8th edition range from 93 to 32%, depending on the number of lymph nodes involved and presence of in-transit or satellite metastases.[2]

For a long time, no additional (systemic) therapy was found to be effective in reducing recurrence and mortality rates in resected high-risk melanoma. However, over the last decade new therapies have become available, first for unresectable stage III-IV melanoma, starting with targeted therapy with BRAF and MEK inhibitors, which have shown encouraging results in these patients.[6-12] Shortly after, immune checkpoint inhibitors against CTLA-4 and PD-1 were introduced and have dramatically changed the landscape of metastatic melanoma treatment.[13-26] Perhaps the spectrum for use of these therapies can be broadened. Therefore, in this review, we will evaluate the effectiveness of immune checkpoint inhibitors and BRAF/MEK inhibitors as adjuvant therapy in resected high-risk melanoma.

ADJUVANT THERAPY

Interferon

Interferon IFN-α-2b was the first and for a long time only therapy approved by the Food and Drug Administration for adjuvant treatment in high-risk melanoma. Its approval in 1995 was mainly based on the results of the ECOG 1684 trial. In this trial both recurrenc- free survival (RFS) and overall survival (OS) were improved in patients treated with IFN-α-2b for 1 year after surgery for T4 or N1 melanomas. Although these results were promising, this treatment did cause severe toxicity and the study was limited by small sample size (n=287).[27]

Two of the largest studies conducted with adjuvant IFN-α-2b were the EORTC 18592 (n=1388) and EORTC 18991 (n=1256). In the EORTC 18952 trial patients with resected stage IIB or III melanoma were randomized to either IFN-α-2b for 13 months, 25 months, or observation. After a median follow-up of 11 years, little effect on the RFS was seen in both treatment arms (13-month arm: hazard ratio (HR) 0.94, p=0,46; 25-month arm: HR: 0.84, p=0.06). No significant effect on OS was observed. Despite these disappointing results, one subgroup did seem to benefit from adjuvant therapy with IFN-α-2b: patients with an ulcerated primary tumor.[28, 29] Subsequently, the EORTC 18991 study randomized patients with resected stage III melanoma to either observation or adjuvant pegylated IFN-α-2b for an intended duration of 5 years. They found a borderline significant better RFS in the pegylated IFN-alpha-2b group of 39.1 versus 34.6% at 7 years (HR 0.87, 95% confidence interval (CI) 0.76-1.00, p=0.055). No advantage in OS was observed and toxicity rates were high, 37% of patients discontinued therapy because of toxicity.[30]

Over the following years several meta-analyses have been performed. These analyses found an advantage in RFS for adjuvant IFN-α-2b in high-risk melanoma, but the advantage in OS was either absent or minor and, therefore, clinically not relevant. Limitations of these meta-analyses were variable inclusion criteria, with different stages of melanoma, and treatment schedules of the included studies. Treatment scheduled differed in dose (low, intermediate or high), induction treatment (with a higher dose and/or more frequent administration of IFN-α-2b), and duration of the maintenance phase.[31-33]

Concluding, slight improvements of RFS and virtually no improvement in OS were seen in patients treated with adjuvant IFN-α-2b. Because of recent changes in the available systemic therapies, IFN-α-2b is outdated and should only be considered as an adjuvant option in countries with limited resources/without access to the new drugs, especially for primary ulcerated melanomas.

Immune checkpoint blockade

The EORTC 18071 study compared high-dose ipilimumab (IPI) 10mg/kg every 3 weeks for four doses and then every 3 months up to 3 years with placebo after complete resection of stage

III (IIIA > 1 mm in SN, IIIB/C, AJCC 7th edition) cutaneous melanoma. This study showed both a convincing 5-year RFS (40.8 vs. 30.3%) and OS (65.4 vs. 54.4%) benefit. Unfortunately, this benefit came with a cost of substantial toxicity: grade 3 or 4 immune-related adverse events occurred (AE) in 41.6% of patients in the IPI arm, compared with 2.7% in the placebo arm and even five (1.1%) of patients died due to immune-related AE.[34, 35]

In an effort to lower these toxicity rates, the three-armed ECOG-1609 trial tested high-dose IPI 10mg/kg versus IPI at the regular dose of 3mg/kg versus IFN-α-2b. Preliminary results suggest that there is no difference in RFS between both IPI arms, with a milder toxicity profile for IPI at 3 mg/kg.[36] Long-term results of this study in terms of RFS of IPI vs. IFN-α-2b and OS results are still pending.

Then, similar to developments in stage IV disease, anti-PD-1 agents were tested in the adjuvant setting. The checkmate 238 study randomized patients who had undergone complete resection of stage IIIB, IIIC, or IV melanoma (AJCC 7th edition) to either anti-PD-1 agent nivolumab (NIVO) 3mg/kg every 2 weeks or high-dose IPI 10mg/kg every 3 weeks for four doses and then every 12 weeks for up to 1 year. They found a 1-year RFS of 70.5% in the NIVO arm and 60.8% in the IPI arm. Toxicity rates were more favorable in the NIVO arm: grade 3 or 4 AEs in 14.4% against 45.9% in the IPI arm. Discontinuation of therapy due to AE occurred in 9.7% of patients in the NIVO group, compared with 42.6% in the IPI group. Therefore, they concluded that adjuvant therapy with NIVO resulted in an improved RFS and a lower rate of severe toxicity, compared with high-dose IPI.[37, 38]

Recently, the EORTC 1325 study, comparing the PD-1 inhibitor pembrolizumab at a fixed dose of 240 mg every 3 weeks with placebo, released its results. This trial was randomized to pembrolizumab or placebo for a total of 18 doses (~1 year) after complete resection of stage III melanoma. The 1-year RFS in patients treated with pembrolizumab was 75.4 versus 61.0% in the placebo group (HR: 0.57, P<0.001) after a median follow-up of 15 months.[39] This study showed a similar rate of grade 3/4 AE of 14.7% when compared with NIVO. These studies show a convincing RFS benefit of adjuvant therapy with immune checkpoint blockade.

BRAF/MEK inhibitors

Another option for treatment in the adjuvant setting is targeted therapy with BRAF and MEK inhibitors. Its use is slightly more limited, as only patients with melanoma harboring a BRAF mutation, which is ~50% of patients, can receive BRAF/MEK inhibitors. Two studies were conducted with BRAF and MEK inhibitors in the adjuvant setting: the BRIM8 and COMBI-AD studies.

The BRIM8 study divided patients into two cohorts: cohort 1 (n=314) included patients with stage IIC, IIIA (SN>1mm) and IIIB melanoma and cohort 2 (n=184) existed of patients with stage IIIC melanoma. In both cohorts patients with $BRAF^{V600}$ mutation-positive melanoma were randomized to receive either vemurafenib or placebo for 1 year, after complete resection of

the tumor. At a median follow-up of 30.8 months in cohort 1 and 33.5 months in cohort 2, an advantage on median disease-free survival (DFS) of vemurafenib was seen in both cohorts. In cohort 2, however, this difference of 23.1 months in the vemurafenib group versus 15.4 months in the placebo group, was not significant (HR: 0.80, 95% CI: 0.54-1.18, p=0.26). In cohort 1 the mean DFS was not reached in the vemurafenib group versus 36.9 months in the placebo group (HR: 0.54, 95% CI: 0.37-0.78, log-rank p=0.001). The authors conclude that the study did not meet its primary DFS endpoints in cohort 2, making the benefit in cohort 1 nonsignificant. The risk reduction in cohort 1 should, therefore, be viewed as exploratory only.[40]

The COMBI-AD study treated patients with a combination of a BRAF and MEK inhibitor. In all, 870 patients with $BRAF^{V600E}$/$BRAF^{V600K}$-mutated, stage III melanoma were randomized to either 12 months of dabrafenib plus trametinib (D+T) or placebo. At a median follow-up of 44 months in the treatment arm and 42 months in the placebo arm, 3- year RFS rates were 59% in the D+T group versus 40% in the placebo group and 4-year RFS was 54 versus 38% (HR 0.49, 95% CI 0.40-0.59). Median RFS was not reached in the D+T arm versus 16.6 months in the placebo arm.[41, 42]

Concluding, these studies show a RFS benefit for the BRAF and MEK combination D+T and suggest a risk reduction for recurrence in patients treated with vemurafenib alone in stage IIC-IIIB melanoma.

Ongoing studies

Currently, three studies involving immune checkpoint inhibitors in the adjuvant setting have not released their results yet: the SWOG S1404, Checkmate 915 and Keynote 716 studies. The SWOG S1404 randomizes patients after complete surgical resection of stage IIIA (N2a), IIIB, IIIC, or IV melanoma among two treatment arms: physician/patient choice of high-dose IFN-α-2b or IPI in arm A and pembrolizumab in arm B.[43] The Checkmate 915 is a randomized phase III study comparing adjuvant combination therapy with NIVO and IPI versus NIVO alone in patients with resected stage IIIB/C/D or IV melanoma (AJCC 8th edition). In both these trials accrual is completed and first results are expected in 2020.[44] Finally, the recently opened Keynote 716 trial randomizes stage II melanoma patients to either a year of fixed-dose pembrolizumab every 3 weeks (maximum of 17 cycles) or placebo. This study is still accruing patients. *Table 1 summarizes all the studies mentioned above.*

Table 1. Overview of adjuvant trials

Study	Design	Stage (AJCC 7th edition)	No. of patients	Median FU	HR RFS	HR OS	2-year RFS	3-year RFS	5-year RFS	IR AE gr 3-4 AE
EORTC 18071	IPI 10mg/kg vs. placebo	IIIA (SN>1mm), IIIB, IIIC	N=951	5.3 years	0,76 (95% CI 0.64-0.89; p<0.001)	0.72 (95% CI 0.58-0.88; p=0.001)	NR? VF: 51% vs. 42%	46.5% vs. 34.8%	40.8% vs. 30.3%	41.6% vs. 2.7%
ECOG-1609	IPI 10mg/kg vs. IPI 3mg/kg vs. HD-IFN	IIIB, IIIC, M1a, M1b	N=1670	3.1 years	NR	NR	NR	54% vs. 56% vs. NR for HD-IFN	NR	57% vs. 36.4% (AE general, most IR)
Checkmate 238	NIVO 3mg/kg vs. IPI 10mg/kg	IIIB, IIIC, IV	N=906	NR, minimum 24 months	HR 0.66, p<0.0001)	NR	62.6% vs. 50.2%	NR	NR	14.4% vs. 45.9%
EORTC 1325	Pembro vs. placebo	III	N=1019	15.1 months	HR 0.57 (98.4% CI 0.43-0.74, p<0.001)	NR	71.4% vs. 53.2% at 18 months	NR	NR	14.7% vs. 3.4%
BRIM8	Vemurafenib vs. placebo	Cohort 1: IIC, IIIA (SN>1mm), IIIB Cohort 2: IIIC	N=498	Cohort 1: 30.8 months Cohort 2: 33.5 months	Cohort 1: 0.54 (95% CI 0.37–0.78, log-rank p=0.0010) Cohort 2: 0.80 (95% CI 0.54-1.18, p=0.26)	NR	62.2% vs. 53.1% Cohort 1: 72.3% vs. 56.5% Cohort 2: 46.3% vs. 47.5%	NR	NR	57% vs. 15% (not IR)
COMBI-AD	Dabrafenib + trametinib vs. placebo	III	N=870	2.8 years	0.49 (95% CI 0.40-0.59; p=0.0006)	0.57 (95% CI 0.42 to 0.79; p=0.0006)**	67% vs. 44%	59% vs. 40%	NR	41% vs. 14%
SWOG S1404	HD-IFN/IPI vs. pembro	III A (N2a), IIIB, IIIC, IV	No results published yet							
Checkmate 915	IPI plus NIVO vs. NIVO	IIIB, IIIC, IIID, IV (AJCC 8th edition)	No results published yet							
Keynote 716	Pembro vs. placebo	II	Accruing patients							

FU: Follow-up; HR: Hazard Ratio; RFS: Recurrence Free Survival; OS: Overall Survival; IR AE: Immune-related Adverse Events; Gr: grade; IPI: Ipilimumab; HD-IFN: High Dose Interferon-alpha-2b; Pembro: Pembrolizumab; * In-transit metastases excluded ** not updated

Another important remaining question for BRAF+ melanoma in terms of adjuvant therapy is: is it better to treat with BRAF/MEK or immunotherapy? No studies have examined this head-to-head yet and it is the question if such a study will ever be performed. For now, choices are being made based on stage IV melanoma experience or cross-trial comparisons, which are always dangerous due to many differences between trials, which do not allow for such comparisons.

Selecting patients

In the studies described above, one of the main inclusion criteria was completely resected melanoma, in most cases consisting of a lymph node dissection. However, this is no longer the standard of care because both the MSLT-II and DECOG-SLT studies showed no survival benefit of CLND compared with the nodal observation by ultrasound.[4, 5] Therefore, lymph node dissections are reserved for clinically detectable lymph node metastasis.

The sentinel node procedure is an important diagnostic tool in determining prognosis, but does it provide enough information if one omits a CLND for a positive SN? The MSLT-II trial showed that additional lymph node metastases were found in 11.5% of patients undergoing a CLND after positive SN. Nonetheless, this does not mean staging would change for all these patients. Additional studies showed that only ~6% of all SN+ cases are upstaged due to additional information provided by the CLND[45]. Moreover, SN tumor burden of more than 1 mm and ulceration of the primary could be an adequate replacement to stratify the risk.[46]

NEOADJUVANT

Neoadjuvant immunotherapy

Besides adjuvant treatment, patients with clinically detectable lymph nodes could also be treated in the neoadjuvant setting, before undergoing the therapeutic lymph node dissection. This could provide some advantages, for example using treatment response as a predictive marker for possible additional adjuvant therapy and reducing presurgical tumor burden. Theoretically neoadjuvant treatment could also allow a stronger immune response to develop, as more tumor antigens will be encountered than in the adjuvant setting.

The phase 1b study comparing neoadjuvant and adjuvant treatment in patients with palpable stage III melanoma was the OpACIN trial. This study randomized 20 patients to either neoadjuvant or adjuvant NIVO 1mg/kg plus IPI 3mg/kg. A high pathologic response rate of 80% was achieved in the neoadjuvant arm and in patients achieving a pathologic response, none had relapsed after a median follow-up of 25.6 months. These promising results came with substantial side effects: grade 3-4 AE occurred in nine out of 10 patients in both treatment arms.[47] Following these findings, the OpACIN-NEO trial was designed examining different neoadjuvant schedules, to reduce toxicity, but preserve efficacy. In arm A

patients received 2x IPI 3mg/kg plus NIVO 1mg/kg every 3 weeks (Q3W); in arm B 2x IPI 1mg/kg plus NIVO 3mg/kg Q3W; and in arm C 2x IPI 3mg/kg Q3W followed immediately by 2x NIVO 3mg/kg Q2W. Accrual to arm C was terminated earlier due to high toxicity rates. In total 86 patients were included in this trial and toxicity profiles were indeed more favorable: grade ≥3 AE occurred in 40, 20 and 50% in arm A, B, and C, respectively. At the same time efficacy was preserved with pathologic response rates of 80 and 77% in arm A and B. To sum up, the dose of IPI 1mg/kg plus NIVO 3mg/kg Q3W would be the most attractive for further research.[48] This is currently happening in an extension cohort: the PRADO study. Patients will be treated with the IPI 1mg/kg plus NIVO 3mg/kg schedule and afterwards only the marked index node will be surgically resected. Depending on the pathologic response subsequent personalized adjuvant treatment with surgery, radiotherapy and/or adjuvant therapy will be performed.[49]

Another study comparing different neoadjuvant treatment schemes was performed by Amaria and colleagues., in which patients received either neoadjuvant NIVO 3mg/kg monotherapy or NIVO 1mg/kg plus IPI 3mg/kg. Accrual was ended early by the Data Safety Monitoring Board due to high toxicity in the combination arm (73% grade 3 trAE) and the observation of disease progression in the NIVO monotherapy arm, preventing surgical resection (2/12 patients, 17%).[50] However, the pathologic complete response rate (pCR) in the combination arm was very similar to the OpACIN and OpACIN-neo studies at 45%.

Neoadjuvant BRAF/MEK inhibitors

Similar to the adjuvant treatment, neoadjuvant studies have been conducted using BRAF and MEK inhibitors in patients with BRAF-mutated melanoma. In a study by Amaria and colleagues, neoadjuvant and adjuvant D+T were combined. Patients were randomized to either surgery or 8 weeks of neoadjuvant D+T, surgery and adjuvant D+T for 44 weeks. The trial was closed to new patient entry after an interim analysis after the inclusion of 21 patients with a median follow-up of 7.1 months showed it was not ethical to assign patients to the standard of care surgery alone. At a median follow-up of 18.6 months an event-free survival of 71% versus 0% was observed with an HR of 0.016 (95% CI: 0.00012-0.14, p<0.001). Pathologic response rates in the neoadjuvant arm were 58% pCR and 17% pathological partial response. Toxicity was similar to previous observations in stage IV disease and did not cause unexpected postoperative complications.[51]

Another study carried out in a slightly different population. Menzies and colleagues performed a phase 2 study in 35 patients with bulky, but resectable stage III melanoma. These patients received D+T for 12 weeks before surgery and continued D+T in the adjuvant setting for 40 more weeks. pCRs were seen in 48% of patients. At a median follow-up of 12.1 months after surgery, 36% patients had relapsed (with a median of 12.9months).[52]

In contrast, the REDUCTOR trial included patients with bulky and unresectable (or high chance of R+) stage III or oligometastatic stage IV melanoma. These patients are treated with neoadjuvant D+T for 8 weeks, after which it is decided whether surgery can be performed on the basis of the evaluation on PET/CT. Interim analyses show that after inclusion of 17 patients with a median follow-up of 22 months, 76% of patients with previous unresectable melanoma could undergo radical surgery. During neoadjuvant treatment, two patients had progressed and were switched to immunotherapy.[53, 54]

Pathologic assessments

An advantage of neoadjuvant therapy is, that it offers the possibility to use the pathologic response as an outcome marker and as a predictor of therapy efficacy for adjuvant therapy. In this light it is important to standardize pathologic assessment and reporting of tumor response. Consensus guidelines have been composed by the International Neoadjuvant Melanoma Consortium and subsequently reported by Tetzlaff and colleagues. In this work, the pathologic response is defined by the % of tumor bed occupied by viable tumor cells (pCR if absent; near pCR if >0% and ≤10%; pathological partial response as ≤50%; and pNR if >50%.[55]

CONCLUSION

After changing the landscape of melanoma stage IV treatment, immune checkpoint blockade and targeted therapy are now also now drastically changing the adjuvant treatment of melanoma. Immunotherapy with anti-CTLA-4 agent IPI showed both a RFS and OS benefit, but at a cost of high severe toxicity rates. Monoclonal antibodies against PD-1 on the other hand showed even better RFS rates, with fewer immune-related AEs. Given these great advantages in RFS, an advantage in OS is expected and these agents will play a big role in adjuvant therapy.

For patients with a melanoma harboring a BRAF-mutation, another option is available for adjuvant therapy: targeted therapy with BRAF and MEK inhibitors. In this area studies have shown an RFS benefit and preliminary data suggests a potential OS benefit.

Besides adjuvant treatment, patients with palpable lymph node metastases have also been included in neoadjuvant studies, with immunotherapy and BRAF/MEK inhibition. These studies show promising results so far and further research is expected in the near future.

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