New approaches and consequences for elderly cancer patients with focus on melanoma

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Chapter 2

New treatment landscape in melanoma: what does this mean for the elderly patient?

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Abstract

The incidence of melanoma in the elderly is rising. Almost 50% of newly diagnosed melanoma patients are above 65 years of age. New effective classes of drugs are available in the metastatic setting. The monoclonal antibodies targeting CTLA-4 and PD-1 inhibit immune checkpoints and can result in long-term disease control. In addition, BRAF and MEK inhibitors, which target protein products of gain-of-function mutations in oncogenes, result in high response rates. Changes in the immune system occur during aging and tumor driver-mutation profiles are age-specific in melanoma. Confronted with an aging population, there is a clear need to incorporate age-specific clinical information into treatment decisions within the new treatment landscape for metastatic melanoma. We therefore reviewed the current treatment options and drugs in development for metastatic melanoma with a special emphasis on the effects in the elderly.

Introduction

Melanoma is the most lethal form of skin cancer. The age-range at diagnosis is wide, with the disease presenting in both very young and very elderly patients. According to the Surveillance, Epidemiology, and End Results database 2009–2013, approximately 47% of patients are ≥ 65 years at diagnosis and a quarter is 75 ≥ years [1]. In order to place age in perspective: in 2011, a 65-year-old inhabitant of the United States of America had a life expectancy of more than 19 years [2].

Until 2010, standard treatment options for metastatic melanoma consisted of dacarbazine and interleukin-2 (IL-2). The landscape of treatment options in metastatic melanoma has changed drastically in recent years, offering these patients effective treatments and even the potential of long-term survival [3]. The immunotherapeutic drugs ipilimumab, a cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody and nivolumab and pembrolizumab, programmed cell death 1 (PD-1) antibodies are now standard of care for melanoma patients [4]. Moreover, in patients with a v-Raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutation, the BRAF inhibitors vemurafenib and dabrafenib and the mitogen-activated protein kinase kinase (MEK) inhibitors trametinib and cobimetinib are now registered drugs. In addition, numerous BRAF and MEK inhibitors and immunologic therapies are in clinical development [5].

Comorbidity and potential side effects influence prescribing behavior in elderly patients, although this is currently largely unsupported by clinical data [6]. In view of the fact that nearly half of all melanoma patients are ≥ 65 years of age, there is a clear need to get specific insight in treatment results in the elderly. The aim of this review therefore is to evaluate the efficacy and

toxicity of current treatment options and promising drugs in development for metastatic melanoma with a special emphasis on the elderly.

Search strategy

Data for this review was identified through a PubMed search and screening of references from relevant articles using the search terms “melanoma”, “elderly”, and “age”. Reports of clinical trials concerning registered drugs in the adjuvant and metastatic setting were also included. Only articles published in English between 1990–2016 were included.

National Comprehensive Cancer Network (NCCN) guideline for Older Adult Oncology version 1.2016 was taken into account, as well as novel instruments rating clinical benefit and value of drugs, developed by the NCCN, the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) [7–9].

Immunologic context in the elderly

For cancer in general, and melanoma in particular, immunologic factors such as expression of immune checkpoint molecules and the balance between pro-inflammatory type 1 T helper cells and anti-inflammatory type 2 T helper cells play an important role in controlling the disease [10]. Reduced immune response, for instance in case of chronic lymphatic leukemia or immunosuppression after organ transplantation coincides with a higher incidence of melanomas [11, 12] with worse outcome [13].

Aging-associated changes in the immune system are steadily being unraveled. For example, age-related hypo-responsiveness of the immune system occurs in later life and develops at a slower rate in women than in men [14]. Aging causes immune senescence, which is related to cumulative DNA damage, and immune exhaustion characterized by T-cells expressing inhibitory checkpoint receptors such as PD-1 [15]. Circulating cytokines generated after cumulative exposure to antigenic stimulation cause a polarization of CD8+ T cells to either a chronic inflammatory state with protective anti-tumor responses, or to an immune tolerant state with poor tumor control [16]. It has been proposed that the activity of regulatory T cells might determine overall immune outcome in elderly melanoma patients [17]: an enhanced regulatory response might further reduce effector responses and the incidence of autoimmunity, whereas a weak regulatory response will facilitate antitumor immunity and increased incidence of autoimmunity. In 200 stage IIB, IIC or III melanoma patients receiving adjuvant interferon (IFN) α2b therapy, the appearance of anti-thyroid, antinuclear, anti-DNA or anticardiolipin autoantibodies and clinical autoimmune manifestations such as vitiligo was associated with better relapse-free and overall survival (OS) [18]. In 52 patients (26%), at least one of these parameters was detected. Seven out of these patients had a tumor relapse, whereas 108 of 146 patients without autoimmune param-

eters had a relapse ($p < 0.001$). This highlights the interaction between autoimmunity and anti-tumor activity.

Guidelines and clinical benefit scales

The NCCN guideline for Older Adult Oncology emphasizes the difficulties in the approach to decision making in the older adult cancer patient [19]. This deservedly includes the important assessment of patients' goals and values regarding the management of their cancer, for example importance of quality of life versus extension of survival. The guideline encourages individual discussion of whether the anti-cancer treatment and associated toxicity profiles fit within the achievement of these goals. In addition, the assessment of risk factors for adverse outcomes from cancer treatment is essential in this decision-making process. Especially comorbidities, geriatric syndromes and socioeconomic issues are considered relevant. The guideline also suggests using tools such as the Chemo Toxicity Calculator or a life expectancy calculator [20, 21]. Melanoma-specific recommendations are only briefly addressed.
Recently, several instruments to rate clinical benefit have been developed. The NCCN include evidence blocks in guidelines [7], the ESMO developed a Magnitude of Clinical Benefit Scale (MCBS) [8] and the ASCO developed a framework to assess the value of cancer treatment options [9]. Rating for anti-melanoma therapies with the NCCN value blocks and ESMO MCBS are shown in Table 1.

Treatment	NCCN efficacy value block [7]	NCCN safety value block [7]	ESMO MCBS [8]
Adjuvant ipilimumab	3	2	-
Dacarbazine	1	3	-
High-dose IL-2	3	1	-
T-VEC for stage III disease	3	4	-
T-VEC for stage IV disease	2	4	-
Ipilimumab	4	2	4
Dacarbazine plus ipilimumab	-	-	3
Nivolumab	4	4	4
Pembrolizumab	4	4	-
Nivolumab plus ipilimumab	5	2	-
Vemurafenib	4	3	4
Dabrafenib	4	3	4
Trametinib	-	-	4
Dabrafenib plus trametinib	4	3	4
Vemurafenib plus cobimetinib	4	3	4
Imatinib	2	3	-

Table 1: Scores for the overall melanoma patient population on the NCCN evidence blocks for efficacy and safety [7] and ESMO MCBS [8].
Scores on the NCCN evidence blocks are given for metastatic stage IV disease and for first-line therapy (except ipilimumab, high-dose IL-2, dacarbazine and imatinib – scores for those drugs are only provided for second-line or subsequent therapy). Efficacy is scored from highly effective (5; often provides long-term survival advantage or has curative potential) to palliative (1; provides symptomatic benefit only), safety from usually no meaningful toxicity (5; uncommon or minimal side effect with no interference with activities of daily living). The ESMO MCBS ranges from 1–5, with treatments scoring 4–5 represent a high level of proven clinical benefit.

Primary treatment

In patients ≥ 70 years of age, time to definitive excision of a primary melanoma is longer than in younger patients [22]. In the same series, the Breslow's thickness was higher in the elderly group and a higher rate of insufficient excision margins were reported, namely 16.8% in the elderly group versus 5% in younger patients ($p < 0.001$). This might be, at least partly, due to the fact that 29% of melanomas in patients ≥ 70 years of age present in the head and neck region versus 8.7% in younger patients. It might be harder to achieve adequate resection margins for this location. In addition, a diminished willingness by elderly to undergo mutilating surgery may explain this difference.

Sentinel-node biopsy based staging not only provides prognostic information for melanoma patients but also increases disease-free survival [23]. A retrospective analysis studied 952 melanoma patients ≥ 75 years of age in whom a sentinel-node biopsy was performed [24]. The median age was 80 years (range 75–99) and median Breslow's thickness was 1.33 mm. In the 380 patients with a melanoma with a Breslow's thickness of < 1 mm, sentinel-node biopsy was performed in 5%. More importantly, a sentinel-node biopsy was performed in only 61% of the 572 patients with a Breslow's thickness ≥ 1 mm. Of the 340 successful procedures, 24% revealed positive sentinel nodes (n = 83). Increasing age was associated with a higher likelihood of a positive sentinel-node: HR 1.09 for 1-year increase in age, p = 0.033. Sentinel-node procedures were performed less frequently when the primary melanoma was located in the head and neck region compared to other regions and less often with increasing age. Complete lymph-node dissection was performed in 76% of patients with a positive sentinel-node, and was performed less frequently with increasing age (p = 0.01). Disease-free survival and OS were superior in patients with a negative sentinel-node compared to patients with no sentinel-node procedure or a positive sentinel-node. Melanoma-specific survival corrected for covariates was inferior with increasing age: HR 1.06 for a 1-year increase, p = 0.048.

These data indicate an unfavorable outcome of primary treatment in elderly melanoma patients compared to their younger counterparts, likely due to multiple factors such as tumor location, patient delay, biological behavior and possibly plain suboptimal treatment.

Adjuvant treatment

The antibody ipilimumab, which blocks CTLA-4, has been evaluated in the adjuvant setting for stage III melanoma [25, 26]. CTLA-4 is an immune checkpoint receptor expressed on T cells. Its physiological function is to prevent autoimmunity, but as a consequence it also prevents immune responses to tumor cells. Patients received 10 mg/kg ipilimumab or placebo every 3 weeks for four cycles and subsequently every 3 months for up to 3 years. In 951 stage III melanoma patients, an intention-to-treat analysis demonstrated a median recurrence-free survival of 26 months (n = 475) in the ipilimumab arm versus 17 months (n = 476) in the placebo group (p = 0.0013). At 5 years, 41% of patients in the ipilimumab group were recurrence-free versus 30% in the placebo group. Overall survival at 5 years was 65% for the ipilimumab group versus 54% for the placebo group. The median age was similar in both groups: 51 years for ipilimumab (range 20–84) and 52 years for placebo (range 18–78) as was the percentage of patients aged < 50 years, namely 45 and 44% respectively. Remarkably, only 18% of patients were ≥ 65 years. No age-specific efficacy or toxicity data were given. 52% of the patients treated with ipilimumab prematurely discontinued treatment due to adverse events versus 4% in the placebo group. In the ipilimumab group, 28% of patients stopped treatment due to disease recurrence compared to 58% in the placebo group. Five ipilimumab-related deaths occurred. The high discontinuation rate in this study containing mainly fit young patients casts

doubt on the feasibility this intense ipilimumab regimen in elderly in general practice.

250 patients with palpable lymph-node involvement of melanoma at presentation and at high risk of relapse were randomized to adjuvant lymph field radiotherapy with 48 Gy in 20 fractions or observation only after lymphadenectomy [27]. A reduction in risk of local relapse from 36% in the observation group to 21% in the radiotherapy group (hazard ratio (HR) 0.52, $p = 0.023$) did not translate into superior relapse-free survival or OS. Unfortunately, no age-specific outcome data was given. The median ages were 58 years (range 22–80) and 56 years (range 22–87) in the radiotherapy and observation groups, respectively.

Dacarbazine

The chemotherapeutic drug dacarbazine was approved by the FDA for the treatment of metastatic melanoma in 1975 and, despite only modest activity, was standard of care until 2010. A meta-analysis showed that, despite higher response rates, more toxic combinational treatment regimen did not lead to improved OS compared to dacarbazine [28]. The largest trial comparing single agent dacarbazine with a combination regimen comprised 231 patients randomized between dacarbazine 1000 mg/m^2 every 3 weeks or the 'Dartmouth-combination' [29]. Median survival was 6.4 months for dacarbazine and 7.7 months for the Dartmouth-combination. The incidence of grade 3–4 bone marrow toxicity, nausea or vomiting and fatigue were higher for the combination regimen. Neither age-specific survival nor age-specific toxicity data are mentioned. The median age was 55 years for patients treated with dacarbazine (range 21–80) and 52 years for the Dartmouth-combination (range 22–77).

Interleukins

Interleukin-2

In 1998, the FDA approved high-dose IL-2 for metastatic melanoma. IL-2 is a T cell growth factor, which in its recombinant form can be administered either subcutaneously (sc) or intravenously (iv). Five randomized trials and 12 single-arm phase II trials with IL-2 were performed before 2007 [30]. None of these trials compared IL-2 alone to dacarbazine or placebo. Instead, other arms contained IL-2 plus histamine dihydrochloride, IFN α-2a or lymphokine-activated killer cells. The IL-2 dosing schedules differed between trials. The median age of patients was not reported in 5 of the 17 trials. Three trials provided age-ranges, namely 20–71 years, 30–69 and 19–62. The remaining 9 trials reported median ages of 42–56. The age ranges indicate a strong selection bias towards young patients.

In 2011, a phase III trial was published in which 185 HLA*A0201 positive patients were randomized between IL-2 alone versus IL-2 plus a gp100-peptide based vaccine [31]. A median progression free survival (PFS) benefit of 2.2 months was observed for the combina-

tion. Although the study was not powered to detect a difference in OS, a trend in favor of the combination-therapy was found: the median OS was 11.1 months for patients receiving IL-2 only and 17.8 months for patients receiving IL-2 plus vaccine (p = 0.06). The mean age was slightly higher in the IL-2 group compared to the combination group (50.3 versus 46.9 years, p = 0.04), but no subgroup analysis for the influence of age on efficacy or toxicity was reported. No maximum age was defined in the inclusion criteria. Unfortunately, no information is available about the age-range of enrolled patients, although the mean ages suggest that participants were mainly non-elderly. Interestingly, all patients ≥ 50 years underwent cardiac stress testing before inclusion to rule out reversible coronary ischemia. Despite this precaution, 27% of patients treated with IL-2 alone and 36% of patients receiving IL-2 plus vaccine had grade 3–5 cardiovascular side effects. For IL-2 monotherapy, 4% arrhythmias and one treatment-related death occurred compared to 19% arrhythmias and two treatment-related deaths in patients treated with the combination. It is unknown whether older patients were excluded or not even considered to participate due to concerns about cardiac toxicity. Overall, grade 3–5 toxicity occurred equally in both groups, namely 80% in the IL-2 group and in 86% in the IL-2 plus vaccine group. This highly toxic profile suggests a restraint policy in incorporating IL-2 to treatment regimens in all patients, including elderly.

Interleukin-21

Interleukin-21 is a cytokine from the IL-2 family of cytokines. An important distinction between IL-2 and IL-21 is that IL-21 decreases CD4+ regulatory T cells in the tumor microenvironment [32]. In a phase II trial, IL-21 was administered iv in three different schedules to 40 metastatic melanoma patients [33]. No complete responses were observed. 22.5% of patients experienced a partial response, with a median duration of 5.3 months, and another 40% of patients had stable disease also lasting 5.3 months. The median age was 56 years (range 25–85). The HR for progression was 0.973 (p < 0.001) for a 1-year increase in age, carefully suggesting that elderly patients have a favorable response to IL-21 treatment. Contrary to IL-2, the side effects of IL-21 were relatively mild: the most common adverse effects were flu-like symptoms and rash, mostly grade 1–2. New clinical trials with IL-21 as a single agent or combined with immune checkpoint inhibitors are ongoing. Because of the mild toxicity profile and suggestion of superior efficacy in the elderly, trials with a large proportion of elderly patients would be clearly of interest.

Intralesional oncolytic virus therapy

Talimogene laherparepvec (T-VEC) is an oncolytic virus carrying two human granulocyte-macrophage colony-stimulating factor (GM-CSF) genes, engineered to invade tumor cells and cause self-destruction. A phase III trial was performed in 436 patients with irresectable stage IIIb–IV melanoma [34] and led to FDA approval in 2015. Eligible patients had at least one injectable cutaneous, subcutaneous or lymph node metastasis ≥ 10 mm, an

LDH ≤ 1.5 the upper limit of normal (ULN) and ≤ 3 visceral metastases with a maximum diameter of 3 cm. Patients with bone or brain metastases were excluded. A 2:1 randomization took place between intralesional T-VEC and GM-CSF sc. The durable response rate, defined as objective response lasting ≥ 6 months, and complete response rate were 16.3% and 10.8% for T-VEC versus 2.1% and < 1% for GM-CSF, respectively. Importantly, in the 131 stage III patients, 33% of the patients treated with T-VEC experienced a durable response. Minor or no differences in durable response rate or OS were found between T-VEC and GM-CSF in patients with ≥ stage IV-M1b disease. OS at 4 years was 33% for T-VEC and 21% for GM-CSF. Treatment-related grade 3–4 toxicity was seen in 11% of the T-VEC-treated patients and in 5% of the GM-CSF treated patients. The only grade 3–4 adverse event occurring in ≥ 2% of patients in the T-VEC group was cellulitis (2.1%). Interestingly, a relatively high number of (very) old patients were included in this trial: the median age was 63 years for T-VEC with 48% of patients ≥ 65 years (range 22–94) and 64 years for GM-CSF with 49% of the patients ≥ 65 years of age (range 26–91). Although age-specific efficacy and toxicity data was not provided, the favorable toxicity profile in this trial with a high density of elderly makes T-VEC of clear interest in elderly patients with stage III and IV-M1a melanoma. The benefit of T-VEC in patients with stage IV-M1b and IV-M1c disease is controversial.

Immune checkpoint inhibitors

Ipilimumab

In 2010, ipilimumab was shown to improve OS in patients with metastatic melanoma [35]. Blockade of CTLA-4 with ipilimumab monotherapy at a dose of 3 mg/kg administered iv every 3 weeks for four cycles as second-line treatment showed a survival benefit of 3.7 months over a gp100-peptide based vaccine. The mean age of patients in this study was 56 years. The HR for death in patients < 65 years treated with ipilimumab monotherapy was 0.65 compared to the vaccine alone, and 0.61 for patients ≥ 65 years of age. Thus, this study found no difference in efficacy between young and older patients. The addition of vaccine to ipilimumab did not improve the survival results. Immune-related toxicity was observed in 61% of patients treated with ipilimumab. The skin was affected in 44% of the patients, but was mainly low-grade. Gastrointestinal toxicity was more severe with diarrhea or colitis in 29% of patients, 7.6% of which experienced grade 3 toxicity. In total, 14 deaths (2.1%) were related to ipilimumab, of which 7 were associated with autoimmunity. No age-specific toxicity data was provided.

A second phase III trial randomized treatment naive patients between dacarbazine 850 mg/m^2 iv plus ipilimumab 10 mg/kg iv and dacarbazine 850 mg/m^2 iv plus placebo [36]. The mean age was 57 years. Dacarbazine plus ipilimumab was superior compared to dacarbazine plus placebo, with a log-HR for death of -0.33 for the whole study population. A log-HR of -0.09 was found for patients ≥ 65 years. Interestingly, the log-HR for death in women < 50 years was -0.56, while it was 0.03 for women ≥ 50 years. This small post-hoc

analysis suggests limited benefit for ipilimumab added to dacarbazine in elderly, possibly ascribable to women ≥ 50 years. At 5 years, 16% of patients with a median age of 58 years (n = 40) were alive in the dacarbazine plus ipilimumab group compared to 8% of patients (n = 20) in the dacarbazine plus placebo groups [37].

A health-related quality of life assessment was performed using the EORTC QLQ-C30 in patients treated with ipilimumab [38]. Post-hoc subgroup analyses for patients < 65 years and patients ≥ 65 years were performed. Baseline parameters were compared to endpoints 12 weeks after initiation of ipilimumab. Ipilimumab treatment resulted in, at most, small impairments in the functional outcomes and symptom scores in patients < 65 years, although it did increase fatigue and appetite loss. Patients aged ≥ 65 experienced moderate impairments in social functioning, global health, fatigue and sleep disturbance. They also had more dyspnea and diarrhea compared to the younger patients.

Ipilimumab extends the median OS by 3.7 months compared to gp100-peptide based vaccine. In addition, importantly, a minority of patients has long-term disease control. Ipilimumab-treated patients surviving > 2 years had a mean age of 59 years, while the mean age of the total ipilimumab-treated group was about 2 years less [39]. This suggests that young patients do not have a higher chance of benefit from ipilimumab treatment. Furthermore, an Italian expanded access study showed that the disease control rate in 188 patients > 70 years of age was with 38% comparable to the 33% in patients ≤ 70 years of age (n = 645) [40]. Although no p-values were given, the ECOG performance status was 0 in 54% of elderly and in 69% of the younger patients. The LDH level was equal in both age groups. Elderly had brain metastases in 9% of cases compared to 20% in patients ≤ 70 years. Despite a lower percentage of performance status 0 for elderly, the median PFS and OS as well as PFS and OS rates at 1 and 2 years did not differ between the age groups. In addition, the safety profile for the elderly was comparable to the wider population, with 36% of elderly patients experiencing a treatment-related adverse event compared to 33% in patients ≤ 70 years of age. The most frequent adverse events among patients > 70 years were pruritus, rash, diarrhea, nausea and liver toxicity.

A pooled analysis of 4,846 patients treated with ipilimumab across 12 clinical studies and a US expanded access protocol did not provide age-specific data on long-term survival [3]. Overall, the 3-year survival rate was a notable 21% and an apparent plateau in the OS curve appeared from thereon.

Despite the fact that induction of immune responses by vaccination is less effective in elderly patients than in younger patients, blocking CTLA-4 seems equally effective in young and elderly patients. Only one trial found a conflicting result especially in women ≥ 50 years of age. Although toxicity data specific for the elderly are limited, some studies suggest slightly increased risk of toxicity in elderly patients.

PD-1 antibodies

The PD-1 receptor is an immune checkpoint molecule expressed on T lymphocytes. When binding to its primary ligand, PD-L1, it becomes activated and thereby negatively regulates the effector response. Thus, expression of PD-L1 by melanoma cells or tumor-infiltrating

macrophages offers a way to escape the host immune response. In 2014, monotherapy with the PD-1 inhibitors pembrolizumab and nivolumab were FDA approved.
A phase III trial with the PD-1 antibody nivolumab (3 mg/kg every 2 weeks) as first-line therapy compared to dacarbazine (1000 mg/m^2 every 3 weeks) in BRAF wild type metastatic melanoma patients showed an OS rate at 1 year of 72.9% in the nivolumab group (n = 210) and 42.1% in the dacarbazine group (n = 208), $p < 0.001$ [41]. Of all included patients, 200 were < 65 years of age, 151 were 65–75 years, and 67 were ≥ 75 years. The HR for death was in favor of nivolumab for all age groups, namely 0.52, 0.44 and 0.25 respectively. It is clearly of interest that higher age seems to correspond with a more favorable HR for nivolumab, possibly because immune exhaustion is more frequent in elderly. Grade 3–4 treatment-related adverse events were 11.7% for nivolumab and 17.6 for dacarbazine. No age-specific toxicity data was given.

Nivolumab was also compared to investigator's choice chemotherapy in a randomized phase III trial for ipilimumab-refractory metastatic melanoma patients [42]. The median age was 59 years for nivolumab (range 23–88) and 62 for chemotherapy (range 29–85). In the per-protocol population of which 120 patients were assigned to nivolumab 3 mg/kg every 2 weeks, 31.7% had an objective tumor response compared to 10.6% of the patients treated with chemotherapy (n = 47). Grade 3–4 treatment-related adverse events occurred in 9% of all 268 patients treated with nivolumab and 3% discontinued treatment because of side effects. No age-related data were reported.
A pooled analysis of 576 patients with a median age of 61 years (range 18–89) treated with nivolumab 3 mg/kg every 2 weeks for metastatic melanoma was performed to study the safety profile [43]. Of them, 38% was ≥ 65 years and 13% was ≥ 75 years. The authors claim the adverse event rate to be 'consistent' with the overall study population for elderly patients: grade 3–4 treatment-related adverse events occurred in 10% of the overall population, in 15% of the patients ≥ 65 years and in 18% of the patients ≥ 75 years.

A phase II study investigating the PD-1 antibody pembrolizumab in ipilimumab-refractory metastatic melanoma enrolled 540 patients [44]. This trial consisted of 3 arms: 180 patients received pembrolizumab 2 mg/kg iv every 3 weeks (median age 62 years, range 15–87), 181 patients received pembrolizumab 10 mg/kg iv every 3 weeks (median age 60 years, range 27–89) or three-weekly investigators choice chemotherapy in 179 patients (median age 63 years, range 27–87). Both pembrolizumab doses were superior to chemotherapy with respect to PFS, with a HR for progression in patients ≥ 65 years of 0.70 (95% CI 0.48–1.01) and 0.60 (95% CI 0.41–0.88) for 2 mg/kg and 10 mg/kg pembrolizumab, respectively. In patients < 65 years the HRs were 0.47 (95% CI 0.34–0.66) for 2 mg/kg and 0.42 (95% CI 0.30–0.59) for 10 mg/kg. The percentage of grade 3–4 adverse events did not differ between the 2 mg/kg pembrolizumab group (11%) and the 10 mg/kg group (14%). Treatment interruption was necessary in 8% of all pembrolizumab-treated patients. Permanent treatment discontinuation due to adverse events was required in 3% of patients that received 2 mg/kg pembrolizumab and in 7% of patients receiving 10 mg/kg.

A phase III trial compared two pembrolizumab dosing-schedules, 10 mg/kg iv once every 2 or once every 3 weeks, to 4 gifts of ipilimumab 3 mg/kg iv in 834 patients [45]. 1:1:1

randomization took place, and median ages for pembrolizumab every 2 weeks, every 3 weeks and ipilimumab were 61 years (range 18–89), 63 years (range 22–89) and 62 years (range 18–88) respectively. For both pembrolizumab-schemes, the HR for PFS and OS were favorable compared to ipilimumab in patients < 65 years as well as in patients ≥ 65 years. Efficacy was similar between the pembrolizumab groups. The most common adverse events for pembrolizumab were fatigue, diarrhea, rash and pruritus. Grade 3-4 adverse events observed in > 1% of pembrolizumab-treated patients were colitis (1.4–2.5%) and hepatitis (1.1–1.8%). Hypothyroidism and hyperthyroidism were more common for pembrolizumab, whereas colitis and hypophysitis were more frequently observed in relation to ipilimumab treatment.

In a phase Ib trial, 655 patients were included and treated with a pembrolizumab schedule of 2 or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks [46]. The median age was 61 years (range 18–64). At baseline, 581 patients had measurable disease. For patients < 65 years, 31.4% (95% CI 26.6–36.5) had an objective response compared to 36.6% (95% CI 30.3–43.2) in patients ≥ 65 years. Unfortunately, no age-specific toxicity data was provided in these pembrolizumab trials.

PD-L1 antibodies

Several antibodies against PD-L1 are in clinical development. A phase I study with the PD-L1 antibody BMS-936559 (or MDX-1105) enrolled 52 melanoma patients [47]. In 17%, an objective response was observed. PFS at 24 weeks was 42%. The age of these patients was not reported except that the minimum age of inclusion was 18 years. Another PD-L1 antibody, atezolizumab, was also evaluated in a phase I trial [48]. 45 patients with a median age of 63 (range 21–83) were treated at various dose levels. Thirty-five were evaluable for response. Of these patients, 26% had a response. PFS at 24 week was 35%. Grade 3–5 adverse events were present in 33% of patients. A phase II trial in 103 metastatic melanoma patients with the PD-L1 antibody pidilizumab showed an OS of 64.5% at 12 months [49]. Most common adverse events were fatigue, diarrhea and arthralgia. No age-related data was given.

Thus, to date only early phase clinical trials have been published regarding PD-L1 blocking therapies. No age-related efficacy or toxicity data are available at this time.

Ipilimumab plus nivolumab

A phase III trial assigned 945 previously untreated stage III–IV melanoma patients to ipilimumab, nivolumab or ipilimumab plus nivolumab in a 1:1:1 ratio [50]. The objective response rate was 19.0% for ipilimumab, 43.7% for nivolumab and 57.6% for the combination ($p < 0.001$ for all comparisons). The PFS was for ipilimumab 2.9 months (95% CI 2.8–3.4), 6.9 months for nivolumab (95% CI 4.3–9.5) and 11.5 months for the combination (95% CI 8.9–16.7). Treatment-related grade 3–4 adverse events were found in 27.3% of patients treated with ipilimumab and led to discontinuation in 13.2%. For nivolumab, it was 16.3% and 5.1% and for ipilimumab plus nivolumab 55.0% and 29.4%, respectively. The mean age of the study participants was 60 years (range 18–90). Although the majority of patients in this trial were < 65 years (59.8%), a notable 1 out of 8 patients was ≥ 75 years.

Unfortunately, no age-specific efficacy and toxicity data were provided. Although the combination clearly has the most favorable efficacy profile, it is also the most toxic regimen. Nivolumab monotherapy has the most favorable toxicity profile and is more effective than ipilimumab alone. Therefore, it might be safer to treat frail elderly with nivolumab monotherapy instead of the combination. However, more data is warranted to further determine the safety of this highly effective combination in elderly patients. The FDA approved this combination for metastatic melanoma in 2015.

Ipilimumab plus sargramostim

A phase II trial included 245 patients that were randomized 1:1 between four cycles of 10 mg/kg ipilimumab every 3 weeks and thereafter once every 12 weeks versus a group with the same ipilimumab schedule combined with recombinant GM-CSF, namely 250 μg sargramostim sc, the first 2 out of every 3 weeks daily [51]. The response rates and PFS did not differ between the groups. However, the OS at 1 year was 68.9% for the combination versus 52.9% for ipilimumab alone (HR 0.64, $p = 0.01$). Patients < 65 years ($n = 138$) had a HR of 0.66 (95% CI 0.41–1.07) and patients ≥ 65 years ($n = 107$) a HR of 0.59 (95% CI 0.30–1.16). Toxicity data was not reported for the different age groups. Interestingly, grade 3–5 toxicity was lower in the combination arm compared to the ipilimumab monotherapy arm (44.9% versus 58.3%, $p = 0.04$). Two fatal adverse events were seen in the combination-arm, and 7 in the arm with ipilimumab alone. The addition of sargramostim might thus protect against ipilimumab-toxicity, which is also of interest for the combination of ipilimumab plus nivolumab.

MAPK inhibition

BRAF inhibitors

Approximately half of the melanomas harbor a gain-of-function mutation in the BRAF gene. There is an inverse-relationship between prevalence of BRAF mutations and age [52]. A cohort of 309 metastatic melanoma patients was tested for BRAF mutation status: all patients < 30 years had a mutation in BRAF, whereas for patients ≥ 75 years this was only 25% ($p < 0.001$) [53]. Although in general 80% of BRAF mutations in melanoma are of the V600E type, the frequency of non-V600E mutations in BRAF, e.g. V600K or V600R, rises with age. In the aforementioned cohort, this was the case in < 20% in patients < 50 years and in > 40% of BRAF-mutated patients ≥ 70 years. This demonstrates that at the DNA level, melanomas in elderly are different from melanomas of younger patients: even within the group of BRAF-mutated melanomas differences exist between old and young patients. Vemurafenib was the first BRAF inhibitor to show OS benefit in a phase III trial [54]. In this study, 675 patients with a positive cobas® 4800 BRAF V600 Mutation Test were randomized between oral vemurafenib 960 mg twice daily and iv dacarbazine 1000 mg/m² every 3 weeks. In total, 655 patients had a V600E mutation in BRAF, 19 a V600K mutation and

one had a V600D mutation. The median age in the vemurafenib-treated group was 56 years (range 21–86) and 52 years (range 17–86) in the dacarbazine-treated group. 512 patients were < 65 years and 160 ≥ 65 years. In all age-groups PFS and OS benefit was shown. The HR for PFS was 0.26 both in patients < and ≥ 65 years. The HR for OS was 0.40 for patients < 65 years and 0.33 for patients ≥ 65 years. In 38% of the 336 patients treated with vemurafenib side effects resulted in dose reductions or interruptions, but it was not reported whether this differed between young and elderly patients. Grade 2–3 photosensitivity was observed in 12% of patients. In this trial, secondary (pre-) malignant cutaneous lesions, such as keratoacanthoma and squamous-cell carcinoma, were observed in 18% of vemurafenib treated patients. Mutations in RAS are seen in 60% of these secondary tumors, most prevalent being HRAS Q61L [55]. These tumors most likely develop from subclinical lesions with pre-existing RAS mutations. Paradoxical activation of mitogen-activated protein kinase (MAPK) signaling during BRAF inhibition results in growth acceleration of the lesions. Since RAS mutations must be present for carcinogenesis, older age might well be a risk factor for this form of specific toxicity due to cumulative DNA damage during life.

In a vemurafenib safety study, 3,222 patients with BRAF V600 mutated metastatic melanoma were enrolled [56]. The median age was 55 years (range 13–95), and 8% (n = 257) were ≥ 75 years. Response rates were equal for this elderly subgroup compared to patients < 75 years. In elderly patients, more high-grade adverse events occurred: 59% (95% CI 53–65) grade 3 and 4% (95% CI 2–7) grade 4 in patients ≥ 75 years compared to 43% (95% CI 42–45) and 3% (95% CI 2–3) in younger patients, respectively. The higher incidence was mainly due to secondary malignant cutaneous lesions: cutaneous squamous-cell carcinoma in 18% versus 6% and keratoacanthoma in 10% versus 6% of patients. Also QT prolongation was found more frequently in the elderly, namely 3% versus <1%.

The BRAF inhibitor dabrafenib also showed a PFS benefit over dacarbazine 1000 mg/m^2 [57]. Out of 250 patients with a V600E mutation in BRAF, 187 were randomized to receive dabrafenib and 63 patients to dacarbazine. Patients with non-V600E mutations in BRAF were excluded. The median age in the dabrafenib group was 53 (range 22–93) and in the dacarbazine group 50 (range 21–82). The estimated PFS was 6.7 months by independent review for dabrafenib and 2.9 months for dacarbazine, with an HR of 0.35 (95% CI 0.20–0.61) in favor of dabrafenib. No sub-analyses for age groups were published, but the authors claim the results “can be generalized” to whole age-range. 28% of patients required dose modification of dabrafenib. Photosensitivity was rare with 3%, all grade 1–2. Secondary keratoacanthoma or squamous-cell carcinoma was seen in 6% of patients. This is lower than in the vemurafenib trials. The authors suggest that this might be due to the relative specificity of dabrafenib for mutated BRAF compared to wild-type BRAF and CRAF – the concentration required for 50% inhibition of kinase activity is five times lower for V600E-mutated BRAF. Eleven percent of patients treated with dabrafenib experienced pyrexia grade 2–3.

In general, agents targeting BRAF mutations are very effective in elderly. Although no head-to-head comparison between the two described BRAF inhibitors has been published,

it seems that photosensitivity and secondary (pre-) malignant cutaneous lesions are more common adverse events of vemurafenib and pyrexia is associated with dabrafenib.

MEK inhibitors

MEK proteins are located intracellular downstream of BRAF in the MAPK pathway. In melanoma patients with a gain-of-function mutation in BRAF, the MEK proteins are activated. Trametinib is an inhibitor of MEK1/2. A phase III trial randomized 322 patients with a V600E or a V600K mutation in BRAF to oral trametinib 2 mg once daily or iv chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks at the discretion of the investigator) [58]. 281 patients had the V600E mutation, 40 the V600K mutation, and one had both. The median age was 55 (range 23–85) in the trametinib-treated group and 54 (range 21–77) for the patients treated with chemotherapy. The HR for progression or death in 251 patients < 65 was 0.44 (95% CI 0.31–0.65) and 0.58 (95% CI 0.29–1.18) in 71 patients ≥ 65 years.

The MEK1/2 inhibitor binimetinib is evaluated in a phase II study in which 30 patients with a NRAS mutation and 41 patients with a BRAF mutation were enrolled [59]. 20% of the NRAS mutated patients had a partial tumor remission and in total 63% of patients experienced disease control. Of the patients with BRAF mutations, 20% had a PR and 51% disease control. No partial responses were seen in the seven patients with BRAF mutation previously treated with a BRAF inhibitor. Median age was 59.5 for the NRAS group (range 45–68) and 57 for the BRAF group (range 45–65). Fifteen patients had to discontinue study treatment due to adverse events, and 33 patients needed dose reduction. No age-specific data for binimetinib are available.

In conclusion for monotherapy with MEK inhibition, only efficacy data for trametinib is currently available pointing to an equal benefit in the elderly population. However, due to an inferior efficacy compared to dual MAPK inhibition, monotherapy should be prescribed only in exceptional cases.

Dual MAPK inhibition: BRAF plus MEK inhibitors

Since vemurafenib, dabrafenib and trametinib all demonstrated improved survival compared to chemotherapy, combinations of a BRAF inhibitor with a MEK1/2 inhibitor were compared to the initial 'standard of care' comprising single agent BRAF inhibition for patients with a BRAF V600 mutation.

One phase III trial demonstrated that the 211 patients treated with dabrafenib plus trametinib had a superior PFS compared to 212 patients that were treated with dabrafenib plus placebo (p = 0.03). Median age in this study was 56.0 years (range 22–89) [60]. The HR for progression was 0.71 in 305 patients < 65 years in favor of the combination, but 1.09 for 118 patients ≥ 65 years of age. However, with longer follow-up the HR for progression in patients ≥ 65 years converted to < 1.0 [61]. An OS benefit was found for dabrafenib plus trametinib in the study population as a whole and for elderly compared to younger patients.

Another phase III trial compared dabrafenib plus trametinib (n = 352) with vemurafenib monotherapy (n = 352) [62]. For 538 patients < 65 the HR for OS was 0.74 and 0.57 for progression in favor of the combination, compared to 0.61 and 0.50 in 166 patients ≥ 65 years of age. Thus, whereas the first study failed to demonstrate a PFS benefit of the combination dabrafenib plus trametinib over dabrafenib alone in elderly, the second study showed both a PFS benefit and an OS benefit of the same combination over single agent vemurafenib. Furthermore, health-related quality of life scores was favorable for the combination compared to vemurafenib alone [63].

A third phase III trial compared vemurafenib plus cobimetinib, a selective MEK inhibitor, with vemurafenib plus placebo [64]. For OS in the whole group, the HR was 0.65 in favor of vemurafenib plus cobimetinib (p = 0.046). The HR for progression was 0.54 in 362 patients < 65 years and 0.45 in 133 patients ≥ 65 years of age. No OS data was provided for these age groups.

In a pooled analysis of 617 patients treated with dabrafenib plus trametinib, an HR reflecting an increment of 10 years of age was calculated for PFS and OS [65]. A multivariate analysis demonstrated that the HR was 0.90 for PFS and 0.89 for OS, which means that elderly patients had a superior survival compared to younger patients treated with the same combination.

Upon resistance to monotherapy with a single-agent BRAF inhibitor, treatment with dual MAPK inhibition using dabrafenib plus trametinib showed less than 15% tumor responses in 71 patients with a median age of 49 years (range 18–82) [66]. The same modest results were obtained by replacing the BRAF inhibitor by binimetinib or trametinib [59, 67].

Therefore, upfront dual MAPK inhibition is recommended and restraint prescription of a MEK1/2 inhibitor, with or without a BRAF inhibitor, after progression on monotherapy with a BRAF inhibitor. For all 3 discussed combination studies, no age-specific toxicity data were given. Most of interest is that the incidence of cutaneous squamous-cell carcinoma was lower in all combination-regimens compared to BRAF inhibition alone. This is an additional argument to prefer combined MAPK-inhibition, especially in elderly patients with a higher risk of cutaneous DNA damage due to sun-exposure.

Imatinib

Imatinib is a tyrosine kinase inhibitor that targets platelet-derived growth factor receptor (PDGFR), stem cell growth factor receptor (cKIT) and stem cell factor (SCF). A cKIT-mutation or amplification is most frequently found in acral and mucosal melanomas, which comprise 6–7% of the melanomas in white populations and over 70% in the Asian population. A phase II trial with imatinib was performed in 43 melanoma patients harboring a cKIT-mutation or amplification [68]. At 8 weeks, 53.5% had either a partial tumor response or stable disease. Fifteen of the progressive patients received a dose escalation of imatinib, which resulted in stable disease for 4 months in one patient. The median age was 57 years (range 27–76) but no age-specific data was shown. In patients ≥ 75 years of age with ad-

vanced gastrointestinal stromal tumor treated with imatinib, drug-related adverse events are reported to be well manageable [69].

Uveal melanoma

The MEK inhibitor selumetinib was studied in patients with metastatic uveal melanoma. This is a rare subtype, characterized by gain-of-function mutations in GNAQ and GNA11 rather than the BRAF and NRAS mutations usually seen in cutaneous melanoma. More than 80% of these tumors harbor such an activating mutation, leading to activation of downstream signaling pathways including the MAPK pathway in an analogous fashion to BRAF and NRAS mutations. The first trial to show clinical improvement in uveal melanoma patients was conducted in 101 metastatic uveal melanoma patients harboring a GNAQ or GNA11 mutation [70]. Patients were randomized 1:1 between selumetinib and temozolomide. The objective response rate was 14% for selumetinib whereas no responses were observed with temozolomide. The median PFS was 15.9 weeks for selumetinib and 7 weeks for temozolimide (HR 0.46, $p < 0.001$). Median OS was respectively 11.8 months and 9.1 months, $p = 0.09$. The selumetinib-group consisted of 50 patients with a median age of 62 (range 32–86), and the temozolomide-arm of 51 patients aged 62 at median (range 34–86). Most common treatment-related adverse events for selumetinib were acneiform rash (75%), creatine kinase elevation (60%), fatigue (57%) and elevation of aspartate aminotransferase (48%) and alanine aminotransferase (47%). In 37% of patients, grade 3–4 toxicity was found and 6% discontinued due to an adverse event. Unfortunately, no age-specific data was provided.

Conclusion

Historical data demonstrates that biological behavior of melanoma differs with ages. Age-related changes of the immune system and an aged microenvironment contribute to a poorer outcome for elderly [17, 71]. Although underrepresentation of elderly in clinical trials still endures [12], it is encouraging that in recent years increasingly such patients are included in metastatic melanoma studies. A notable exception is the trial studying ipilimumab in the adjuvant setting, in which over 80% of the participants were younger than 65 years of age [25]. Efficacy in elderly with metastatic melanoma is demonstrated for all FDA approved treatments. It is exciting that – in contrast to results of vaccination for infectious diseases – activation of the immune system in elderly can be achieved with immune checkpoint inhibitors resulting in antitumor efficacy. Unfortunately, age-specific toxicity data is scarce. Apart from the limited toxicity data for elderly, outcome data for metastatic melanoma treatment is increasingly reported and looks promising for this potentially vulnerable subgroup.

The NCCN evidence blocks summarize information on treatments with respect to efficacy, safety, quality of evidence, consistency of evidence and affordability [7] and the ESMO MCBS provides an overall grading about the level of proven clinical benefit, corrected for toxicity [8]. These outcomes are based on available studies for the entire population. Interestingly, the outcome for many newly registered melanoma drugs (or combinations) obtained high scores for clinical effect in the NCCN value blocks and ESMO MCBS (see Table 1). This indicates a meaningful clinical benefit of several drugs and underscores the relevance to seriously consider these novel treatment approaches in the elderly. Other aspects that should be taken into account are summarized in the NCCN guideline for Older Adult Oncology [19]. Moreover, several ongoing approaches will, in the near future, give better insight into the effects of the novel melanoma drugs in the elderly. Reports of real-world data from expanded access trials, compassionate use programs or public sources can partly reduce the knowledge gap. In addition, the FDA and European Medicines Agency pharmacovigilance databases can be interrogated for age-related side effects [72, 73]. In 2015, ASCO released a series of recommendations to improve the generation of evidence in older cancer patient treatment [74]. The FDA has implemented an initiative named Drug Trials Snapshots in which data from clinical trials is made transparent with regards to age, gender and ethnicity of the participants [75]. In addition, descriptions of differences in efficacy and toxicity for the same demographic subgroups are provided. All these initiatives will support physicians' and researchers' access to the clinical treatment data of elderly cancer patients. Ideally, sufficient data regarding effects in the elderly would enable development of evidence-based scoring tools to support physicians and patients in the decision-making process of melanoma treatment.

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