The role for chemotherapy in the modern management of melanoma

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Practice points

- Dacarbazine remains the only US FDA- and EMA-approved chemotherapy drug for treating advanced malignant melanoma.
- Carboplatin plus paclitaxel combination chemotherapy has also been widely used, with evidence of efficacy as both first- and second-line treatment.
- Combination chemotherapy regimens and biochemotherapy have both shown improved response rates compared with dacarbazine, but no difference in overall survival.
- Novel chemotherapy agents have failed to live up to early promising results seen in Phase II trials.
- Chemotherapy may increase the effectiveness of immunotherapy and targeted therapies when used in combination.
- Chemotherapy has demonstrated efficacy in patients with mucosal melanoma, as well as those who have progressed on immunotherapy/targeted therapy.

The treatment of malignant melanoma has changed beyond recognition in the last 7 years. Where previously single agent dacarbazine was often the only treatment used for advanced disease, now there are potentially multiple lines of treatment, based on immunotherapy and targeted treatment options, either as monotherapy or in combination. In this brave new world the question arises, does chemotherapy still have any relevance in the modern management of melanoma? In this review, we summarize the various chemotherapeutic options that have been trialled in melanoma to date, and discuss the role chemotherapy may still play in treating melanoma, potentially in combination with more novel agents, or in certain subtypes of melanoma.

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The prognosis with advanced melanoma (unresectable stage III and stage IV) has improved dramatically over the last 7 years. Prior to this, the expected median overall survival (OS) with palliative chemotherapy was approximately 9 months [1]. With recent advances in immunotherapy and targeted therapy the median OS for advanced melanoma has improved to 20–30 months [2].

Chemotherapy was the backbone of systemic treatment for advanced melanoma for many years. In the 1960s, intra-arterial melphalan was described as the most effective systemic treatment, but it was limited by its high toxicity and short duration of action [3]. In the 1970s, dacarbazine was established as the new standard of care treatment, and in most countries it remains the only approved chemotherapy agent for treating advanced melanoma. Many other drugs have been used off-label, including temozolomide, paclitaxel, docetaxel, cis/carboplatin and nitrosoureas. No single chemotherapy agent or combination has demonstrated an improvement in OS in randomized trials. However, a minority of

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patients have some palliative benefit from chemotherapy, with reported objective response rates (ORR) of 5–20% [4]. In the 1990s high-dose interleukin-2 (IL-2) was approved by the US FDA for use in highly selected patients, after demonstrating an ORR of 16%, with durable responses and an improvement in OS in 40% of responders [5]. A meta-analysis of IL-2 therapy in melanoma over a period of 30 years confirmed an ORR of 16.5%, with a complete response (CR) rate of 4%, but the use of IL-2 remains limited due to its significant toxicity [6].

Since 2010 the treatment of advanced melanoma has been revolutionized, as a result of understanding the key role of the MAPK signaling pathway in melanoma, and unlocking the molecular basis of controls of the immune system. The immune-checkpoint CTLA-4 inhibitor ipilimumab was the first drug to demonstrate improved OS in advanced melanoma [7], with an ORR of 19% when used first-line [8] and 3-year survival rate of 22% [9]. The newer PD-1 checkpoint inhibitors pembrolizumab and nivolumab have proven even more effective, with ORR of 40 and 44%, respectively [8,10–12]. All three drugs are now licensed for use as first-line treatment for advanced melanoma. The combination of ipilimumab and nivolumab was also recently licensed for treating metastatic melanoma, with an improved ORR of 58%, but also added toxicity (55% of patients developed grade 3/4 toxicity) [13]. There also remain no well-established predictive biomarkers for selecting which patients are most likely to respond to these drugs [14].

Mutations in the *BRAF* gene are present in about 40% of cutaneous melanomas, resulting in a mutated BRAF protein, which drives tumor progression through constitutive activation of the MAPK pathway [15]. For these patients the development of targeted BRAF inhibitors such as vemurafenib and dabrafenib has had a further significant impact on survival, with a 50% ORR, including efficacy in patients with bulky metastatic disease [16,17]. However, median duration of response is approximately 7 months, after which resistance develops via a number of mechanisms [18]. MEK inhibitors, which act downstream of BRAF to inhibit the activity of MEK1/2, increase response rates and delay development of resistance when combined with BRAF inhibitors, with the combination of dabrafenib plus trametinib demonstrating an ORR of 64–69%, median progression-free

survival (PFS) of 11 months, median OS of 25 months and 3-year OS rate of 44% [19–21]. Grade 3/4 toxicity is comparable to monotherapy treatment, affecting around 35% of patients [19]. Combined BRAF and MEK inhibitor therapy is now the new standard of care for targeted therapy in *BRAF* mutant melanoma.

The new era of immunotherapies and targeted treatments have significantly improved survival for patients with advanced melanoma, as summarized in Table 1, with 1-year OS rates of around 74% with BRAF plus MEK inhibitor therapy and 73% with ipilimumab plus nivolumab, compared with about 42% with conventional chemotherapy [22]. However, targeted therapies can only be used in about half of melanoma patients, that is, those with a *BRAF* mutation, with development of resistance almost inevitable at some point. Immunotherapy activity is independent of *BRAF* status. However, despite these major advances, overall about half of patients with advanced melanoma still die within 2 years, and so there remain significant challenges for treatment of this disease.

Both BRAF/MEK inhibitors and immunotherapy also have limited efficacy in certain subgroups of melanoma including mucosal and uveal melanoma. In mucosal melanoma *BRAF* mutations are less common than in cutaneous melanoma, found in about 10% of cases [28]. Mutations or amplifications of *C-KIT* are more common, present in up to 39% of mucosal melanomas [29], with response to the tyrosine kinase inhibitor (TKI) imatinib seen in this population, but only in the 10–15% of tumors with mutated *KIT* (partial response in 54% of patients treated) [30]. In patients with amplified *KIT* there were no responses, although stable disease (SD) was seen in 2 of 11 patients (18%) [30]. Trials are ongoing of other TKIs, including nilotinib (the NICAM study) and PLX3397 (the PIANO study). Immunotherapy is less effective in mucosal melanoma, with ORR of 7–12% with ipilimumab, 23% with nivolumab and 37% with combination nivolumab plus ipilimumab therapy [31,32]. Uveal melanoma also has a different biology to cutaneous melanoma, with constitutive activation of the MAPK pathway driven by *GNAQ/GNA11* mutations rather than *BRAF* in the majority of cases [33]. MEK inhibitors have been investigated in uveal melanoma, as described in more detail later, with the MEK1/2 inhibitor selumetinib demonstrating ORR ranging from 3–14% [34,35]. Both mucosal and uveal melanoma have a low

Table 1. Summary of key systemic therapies for advanced cutaneous melanoma.

Treatment	Dose	Line	ORR (%)	DCR (%)	Median PFS (months)	Median OS (OS rate %)	G3/4 toxicity (%)	n	Ref.
Dacarbazine	1000 mg/m ² , every 21 days	1st	10–14	33–36	2.2	9–11 months (1-year OS: 38–42)	18–29	638	[11,23]
Temozolomide	150 mg/m ² /day, 7 of every 14 days	1st	15	38	2.3	9 months (1-year OS: 34)	35	429	[23]
Paclitaxel	80 mg/m ² , 3 of every 4 weeks	1st	4	49	1.9	11 months	34	326	[24]
Carboplatin + paclitaxel	AUC5 + 175 mg/m ² , every 21 days	1st	16	–	4.4	9 months	45	71	[25]
Carboplatin + paclitaxel	AUC6 + 225 mg/m ² , every 21 days	1st	18	57	4.2	11 months	78	413	[26]
Carboplatin + paclitaxel	AUC6 + 225 mg/m ² , every 21 days	2nd	11	62	4.2	10 months	70	135	[27]
Ipilimumab	3 mg/kg, every 21 days × 4 cycles	1st/2nd	12–19	28	2.9	11 months (3-year OS: 21)	20–27	278	[7–9,13]
Nivolumab	3 mg/kg, every 14 days, until disease progression	1st	44	57	5.1–6.9	– (1-year OS: 73)	12–16	526	[8,11,13]
Pembrolizumab	10 mg/kg, every 21 days, until disease progression/2 years	1st	40	47	4.1 [est]	– (1-year OS: 68) (est)	10	277	[10,12]
Ipilimumab + nivolumab	Ipi 3 mg/kg + Nivo 1 mg/kg, every 21 days × 4 cycles, then Nivo 3 mg/kg, every 14 days, until disease progression	1st	58	71	11.5	– (1-year OS: 73)	55	314	[8,13,22]
Dabrafenib + trametinib	150 mg BD + 2 mg OD	1st	64–69	90–93	11–11.4	25 months (1-year OS: 72–74)	32–52	563	[19–21]

AUC: Area under the Curve; BD: Twice daily; DCR: Disease control rate (complete response + partial response + stable disease); n: Number treated in key trials; OD: Once daily; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

mutation burden compared with cutaneous melanoma [33,36]. This could be partially responsible for the emerging evidence of poor response to checkpoint inhibitors, with the response in mucosal melanoma described above and ORR of 3–5% in uveal melanoma [37,38].

We previously published a review on the role of chemotherapy in the modern management of melanoma [39]. Three years on, we now provide an update, including new chemotherapy agents, novel combination regimens that could increase the efficacy of traditional chemotherapy drugs and a review of the role of chemotherapy in specific subgroups of melanoma that are less responsive to the newer immunotherapy and targeted agents.

Single-agent chemotherapy

Dacarbazine, also known as dimethyl-triazenoimidazole-carboxamide, had been the standard

of care systemic treatment for advanced melanoma since the 1970s. It is an alkylating agent and a prodrug that requires conversion in the liver into the active compound 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide. The approval of dacarbazine has always been controversial as there are no randomized trials showing OS benefit compared with best supportive care. Dacarbazine has been used as the comparator arm in most trials of newer agents, and a pooled analysis of 23 randomized trials showed a wide range of ORR but an average of 15% as a first-line treatment [40]. Most of the responses are partial (11%) and rarely durable, but some cases of complete response have been reported (4%), which may have impact on survival in these rare cases. Dacarbazine is given at a dose of 800–1000 mg/m² and is administered intravenously every 3–4 weeks. It is usually

fairly well tolerated, with grade 3/4 toxicity reported in about 18% of patients [11]. The most common toxicities are nausea, vomiting, myelosuppression and fatigue.

Temozolomide is another alkylating agent and a derivative of dacarbazine, which also needs converting in the body to its active form, but in this case conversion is spontaneous and occurs in all tissues at physiologic pH. Despite not being licensed in melanoma, it is widely used in many countries. Two large Phase III randomized trials compared temozolomide and dacarbazine as first-line cytotoxic treatment in melanoma patients without brain metastasis, and concluded they are overall equivalent, with no significant differences in safety profile or OS [23,41]. The main differences compared with dacarbazine are that temozolomide is administered orally and is able to cross the blood–brain barrier. Dacarbazine is ineffective in treating brain metastases, while temozolomide has proven to have some limited activity in a Phase II trial, with an ORR in the brain of 6% and stabilization of the brain disease in 27% of cases [42]. Temozolomide is most commonly administered orally at a dose of 200 mg/m² for 5 days every 4 weeks and is therefore more convenient to administer compared with dacarbazine, but is more reliant on patient compliance.

Fotemustine is a nitrosourea that started as a quite promising drug with a reported ORR of 24% and high activity in brain metastases (ORR of 25%) [43]. A randomized Phase III trial comparing fotemustine with dacarbazine showed an ORR of 15 versus 7%, respectively ($p = 0.043$), with 6 versus 0% response in brain metastases. However, there was no significant benefit in PFS or OS and half of patients treated with fotemustine had grade 3/4 hematologic toxicity [44]. Thus it is not commonly used in the treatment of melanoma. A study of intravenous versus hepatic arterial infusion of fotemustine in patients with uveal melanoma and unresectable liver metastases was stopped early due to poor accrual (NCT00110123).

The platinum compounds carboplatin and cisplatin have been investigated in a number of Phase II trials in melanoma. As single-agent treatment in chemotherapy-naïve patients, carboplatin has demonstrated an ORR of 19% [45], and cisplatin an ORR of 16% [46]. In a Phase II trial of cisplatin combined with WR-2721 (an organic thiophosphate thought to protect normal tissues from cisplatin toxicity) in 36 patients the

ORR improved to 53%, although the median duration of response was only 4 months [47]. However, a larger randomized Phase II trial of this combination found an ORR for the combination of 23%, with greater toxicity than cisplatin alone, so this combination has not been explored further in melanoma [46].

Paclitaxel as a single agent has been investigated since the 1990s in multiple trials, generally on a weekly schedule of 80 mg/m² (3 weeks on, 1 week off), with an ORR ranging from 3 to 17% [39]. In the SYMMETRY study, a Phase III trial with 651 patients randomized 1:1 to paclitaxel alone or paclitaxel plus a proapoptotic drug called elesclomol, the ORR with paclitaxel alone was 4% [24]. The ORR with paclitaxel plus elesclomol was higher (7%), but the study closed early due to early indications of poorer OS in some patients in the combination arm [24]. Paclitaxel is more commonly used in combination chemotherapy regimens for melanoma, as described below.

Combination chemotherapy

Carboplatin plus paclitaxel (CP) has been assessed as both first-line and second-line chemotherapy treatment for advanced melanoma. In the BEAM study, a randomized Phase II trial of CP versus CP plus bevacizumab as first-line treatment for advanced melanoma, the ORR was 16.4 and 25.5%, respectively (with no significant difference in PFS or OS) [25]. CP has been used as the control arm in two Phase III trials in patients with advanced melanoma, compared against the experimental arm of CP plus sorafenib. In the first-line setting CP demonstrated an ORR of 18%, median PFS of 4.2 months and median OS of 11.3 months [26]. In the second-line setting, the ORR for CP was 11%, median PFS was 4.2 months and median OS was 10 months [27]. In both trials there was no significant benefit seen with adding sorafenib. Due to the modest activity of CP as both first-line and second-line chemotherapy, this combination, although not licensed, is widely used in advanced melanoma.

Carboplatin plus nab–paclitaxel has been tested in a Phase II trial, which showed an ORR of 26% and median PFS of 4.5 months in 41 chemo-naïve patients, and an ORR of 9% and median PFS of 4.1 months in 35 previously treated patients with metastatic melanoma [48]. Similar results have been found in a study of the same combination in a Chinese population, with an ORR of 20% in chemo-naïve patients and

6% in previously treated patients [49].

The Dartmouth regimen is a combination of dacarbazine, cisplatin, carmustine and tamoxifen. In a Phase III trial with 240 patients randomized to either the Dartmouth regimen or standard dacarbazine, ORR and OS were higher in the combination arm, but the difference was not statistically significant, with an ORR of 18.5 versus 10.2%, respectively ($p = 0.09$), OS of 7.7 versus 6.3 months ($p = 0.52$), respectively, and more toxicity with the combination chemotherapy [50]. Similar results were seen in a second Phase III trial comparing the Dartmouth regimen with dacarbazine plus interferon (IFN) [51].

The CVD regimen is a triplet combination regimen of cisplatin, vinblastine and dacarbazine. The initial Phase II study with 52 patients showed an ORR of 40% and OS of 12 months in the responders, but also significant toxicity (hematologic, gastrointestinal and peripheral neuropathy) [52]. This regimen has since been used with IL-2 and IFN- α to develop biochemotherapy regimens, as noted below.

Modern chemotherapy agents

A number of newer chemotherapy agents have shown promising results in Phase II trials in melanoma, but have failed in Phase III trials, either due to safety concerns or lack of improved efficacy. Some of the key agents that have been investigated are summarized in this section:

Nab-paclitaxel (ABI-007, Abraxane) uses nanoparticle albumin-bound (nab) technology as a vehicle for the delivery of paclitaxel, and was originally developed as a Cremophor-free formulation of paclitaxel, thus avoiding the adverse reactions associated with the Cremophor solvent used to administer conventional paclitaxel. Promising Phase II data led to a Phase III trial where 529 patients were randomized to either nab-paclitaxel or dacarbazine [53]. Nab-paclitaxel showed an ORR of 15 versus 11% with dacarbazine ($p = 0.239$), and nearly doubled the primary end point of PFS, from 2.5 to 4.8 months (HR: 0.792; $p = 0.044$) [53]. However, there was no significant difference in OS (12.6 months with nab-paclitaxel vs 10.5 months with dacarbazine; HR: 0.897; $p = 0.271$), although this may have been affected by the high rate (75%) of poststudy treatments, such as BRAF inhibitors and ipilimumab (equivalent use in both arms) [53]. There was also significantly higher grade 3/4 neuropathy with

nab-paclitaxel (25 vs 0% with dacarbazine).

DHA-paclitaxel is another formulation of paclitaxel, conjugated to a natural fatty acid, docosahexaenoic acid (DHA) via an ester bond, which targets paclitaxel to tumor cells over normal cells, allowing higher concentrations of paclitaxel to be delivered to tumor cells for a prolonged period of time [54]. Again, despite promising Phase II data, with an ORR of 10% and median OS of 14.8 months, the subsequent Phase III trial, which randomized 393 chemonaïve patients with metastatic melanoma to either DHA-paclitaxel or standard dacarbazine, found no differences in ORR, PFS or OS and increased myelosuppression with DHA-paclitaxel [55].

Elesclomol is an agent that promotes cell arrest and apoptosis by increasing the oxidative stress in cancer cells [56]. Its activity in melanoma has been assessed in combination with paclitaxel in two main trials. A Phase II randomized trial compared single-agent paclitaxel with the combination and reported an ORR of 3 versus 15%, respectively, with an increase of PFS from 56 to 112 days [57]. However, as noted above, in the subsequent Phase III SYMMETRY trial using the same treatment arms recruitment was halted early due to an interim subgroup analysis indicating poor prognosis patients with a raised lactate dehydrogenase level had significantly worse OS in the experimental arm (6.0 vs 7.8 months in the control arm) [24]. In the 651 patients randomized, all chemotherapy-naïve, there was no evidence of increased efficacy from combination treatment, with the ORR 7% in the combination arm versus 4% with paclitaxel alone ($p = 0.12$) and the median OS 6.0 months versus 7.8 months, respectively ($p = 0.04$) [53].

Tasisulam (LY573636) is a small molecule inhibitor with both antiangiogenic and proapoptotic characteristics. Although its exact mechanism of action is not fully established, it appears to inhibit cell-cycle progression at the G2 checkpoint and act via the intrinsic apoptotic pathway, causing caspase-dependent cell death [58]. In a Phase II trial with 68 previously treated melanoma patients single agent tasisulam demonstrated an ORR of 11.8% (90% CI: 5.3–18.2%), a PFS of 2.6 months and an OS of 9.6 months [59]. However, a subsequent Phase III trial comparing tasisulam with paclitaxel was terminated early due to safety concerns after more treatment-related deaths were noted in the experimental arm compared with the control

arm (13 vs 0) [60]. Analysis of the 336 patients randomized suggested tasisulam was unlikely to be superior than paclitaxel, with an ORR of 3 versus 4.8% and an OS of 6.77 versus 9.36 months [60].

Allovectin-7 is a DNA plasmid administered as an intratumoral injection, developed with the aim of reversing the downregulation of HLA class I/II MHC molecules by melanoma cells, by which they avoid immunosurveillance [61]. In Phase II trials allovectin-7 injections produced a local response in 9–12% of patients, with 21% of patients with stage IV disease also showing a response in a noninjected site [62–64]. However, in a Phase III trial allovectin-7 was found to be inferior to standard chemotherapy (dacarbazine or temozolamide), with the primary end point of ORR at ≥ 24 weeks 4.6% with allovectin-7 versus 12.3% with chemotherapy, and a correspondingly shorter OS of 19 versus 24 months [65].

Biochemotherapy

Single agent immunomodulating agents such as IFN- α and IL-2 have shown some clinical activity in melanoma, but have now largely been superseded by the checkpoint inhibitors detailed in the Introduction. As noted above, high-dose IL-2 is approved by the US FDA for the treatment of advanced melanoma. However, it is associated with significant treatment-related toxicity and so is generally only used for selected patients in specialist centers experienced at administering it. Many different chemotherapy agents have been used in combination with IFN- α or IL-2 (collectively termed biochemotherapy regimens), including dacarbazine, temozolamide, cisplatin, vinblastine and carmustine, with variable results. A meta-analysis of 18 trials of biochemotherapy reported higher ORR when compared with chemotherapy alone, yet no significant improvement in OS [66]. The combination of chemotherapy with immune checkpoint inhibitors is discussed separately below. Adoptive T-cell strategies use chemotherapy, either alone or in combination with radiotherapy, to lymphodeplete patients prior to infusing tumor-infiltrating lymphocytes, and have been shown to produce durable complete responses in about 20% of heavily pretreated patients [67].

Overall, as summarized in a systematic review of 41 randomized clinical trials, both combination chemotherapy regimens and

biochemotherapy regimens have demonstrated comparable, or in some cases increased response rates, but no significant improvement in OS, compared with single-agent dacarbazine treatment [68].

Chemotherapy combined with checkpoint inhibitors

Following the development of effective checkpoint inhibitors, the combination of traditional chemotherapy with these newer immunotherapy agents has been investigated. Potential synergy between chemotherapy and immunotherapy is based on two main factors. First, chemotherapy-mediated apoptotic tumor cell death leads to the release of tumor antigens, which can then potentially be recognized by cytotoxic T lymphocytes [69]. Second, chemotherapy has been shown to modify the tumor immune micro-environment in many ways, including reduction of immune-suppressive regulatory T cells (Tregs) and promotion of the activity of dendritic cells and cytotoxic T cells [70]. In cutaneous melanoma a large Phase III randomized, double-blind study of dacarbazine 850 mg/m² plus ipilimumab 10 mg/kg versus dacarbazine plus placebo found combination treatment improved OS compared with chemotherapy alone, with a median OS of 11.2 versus 9.1 months (HR: 0.72; $p = 0.0009$) and 5-year survival rates of 18.2 versus 8.8%, respectively [71,72]. There was a different toxicity profile compared with ipilimumab monotherapy, with less diarrhea and colitis (despite the higher dose of ipilimumab used), but more grade 3 hepatotoxicity. There has not been a large Phase III trial comparing combination treatment with ipilimumab monotherapy, but a small Phase II trial of ipilimumab 3 mg/kg plus dacarbazine versus ipilimumab monotherapy found some additional benefit to adding chemotherapy, with ORR of 14.3 versus 5.4%, and 3-year survival of 20 versus 9% [73]. However, it is worth noting that ipilimumab in this study was administered every 4 weeks rather than the usual 3-weekly regimen, which may explain why outcomes in the ipilimumab monotherapy arm were poorer than those reported in other studies. Grade 3/4 toxicity was 17.1 versus 7.7% [73]. Thus ipilimumab/dacarbazine combination treatment is generally not used. There have not been any trials published investigating PD-1 inhibitors in combination with chemotherapy in melanoma, as this area has generally been superseded by anti-CTLA-4 and anti-PD-1

combination therapy.

Chemotherapy combined with targeted agents

There is evidence that combining chemotherapy with MEK inhibitors can be more effective than chemotherapy alone. In *BRAF* V600E mutant melanoma, a Phase II study of selumetinib plus dacarbazine showed an improvement in PFS over dacarbazine alone (5.6 vs 3.0 months, respectively, HR: 0.63; 80% CI: 0.47–0.84; $p = 0.21$), and also better ORR (40 vs 26%, respectively), but no significant difference in OS (13.9 vs 10.5 months, HR: 0.93; 80% CI: 0.67–1.28) [74]. In *BRAF* wild-type melanoma, which has more limited treatment options, a Phase II study of selumetinib plus docetaxel did not find a significant difference in PFS over docetaxel alone (4.2 vs 3.9 months, respectively, HR: 0.75; 90% CI: 0.50–1.14; $p = 0.130$) [75]. However, there was a difference in ORR of 32 versus 14%, which almost reached statistical significance ($p = 0.059$), suggesting the combination of taxanes and MEK inhibitors for treating *BRAF* wild-type melanoma is worth investigating further, with patient selection ideally driven by better predictive biomarkers. It remains to be seen whether other MEK inhibitors might achieve better results, considering trametinib, unlike selumetinib, has shown a survival advantage over chemotherapy in *BRAF*-mutated melanoma and has potentially superior pharmacokinetics, including a longer half-life. A randomized Phase II study investigating trametinib in combination with paclitaxel chemotherapy is ongoing (EudraCT number: 2011-002545-35). Initial results look promising, with a response rate with the combination of 40% (6 of 15 patients treated in the dose escalation phase of this study) [76].

Preclinical studies suggest that the combination of the *BRAF* inhibitor vemurafenib with the chemotherapy drugs temozolomide and fotemustine increases cell death, with a tendency to increased apoptosis when vemurafenib was added sequentially, 72 h after chemotherapy, rather than concurrently [77]. However, there have not been any clinical trials published investigating *BRAF* inhibitor and chemotherapy combination treatment.

Chemotherapy for specific melanoma subgroups

• Advanced mucosal melanoma

Mucosal melanoma accounts for about 1% of all melanomas in a Caucasian population,

although the proportion is much higher, up to 23%, in a Chinese population. Mucosal melanomas generally confer a poorer prognosis compared with all other subtypes of melanoma, with similar survival outcomes between different sites of origin, the most common of which are head and neck, anorectal and vulvovaginal [78]. The rarity of mucosal melanoma means data on efficacy of systemic treatments are limited. However, in clinical trials, the response rate to the PD-1 inhibitor nivolumab has been about 23% and to ipilimumab/nivolumab combination treatment about 37% [32]. Treatment options for these patients are limited. *BRAF* mutations are less common (~10% of mucosal melanomas, compared with approximately 40% of cutaneous melanomas) [28]. Mutations or amplifications of *C-KIT* are more common, present in up to 39% of mucosal melanomas [29], with reported ORR of 29% to the TKI imatinib in patients with an activating mutation [30]. Trials of other TKIs are ongoing, including nilotinib (NICAM study, NCT01395121) and PLX3397 (PIANO study, NCT02071940). However, a significant number of patients with mucosal melanoma will not have an actionable mutation, and, as immunotherapy is known to be less effective in this treatment group, chemotherapy treatment remains an important treatment option.

A retrospective multicenter analysis of 95 patients with untreated advanced melanoma in South Korea found response rates of 26% to first-line dacarbazine-based chemotherapy, with no significant difference between patients with cutaneous and noncutaneous melanoma [79]. Similarly, in a retrospective review of 32 patients, carboplatin (AUC5) plus paclitaxel 175 mg/m² every 3 weeks demonstrated efficacy after failure of a median of three previous systemic therapies in patients with both cutaneous ($n = 10$) and noncutaneous metastatic melanoma, including mucosal melanoma (again $n = 10$), with a response rate of 22% and no significant difference between cutaneous and noncutaneous cases [80]. Median PFS was 2.5 months and OS was 5.3 months. Biochemotherapy has been shown to produce higher response rates of 36–47%, but no significant difference in OS [66].

• Advanced uveal melanoma

Uveal melanoma, although rare, is the most common primary malignant tumor of the eye in adults, representing 3–5% of all melanoma

cases [81]. Treatment of this primary tumor prevents local recurrence in about 95% of cases, but half of patients will go on to develop metastatic disease [82]. Advanced uveal melanoma commonly metastasises to the liver (89%) and lungs (29%), and is generally treatment refractory, resulting in a high mortality rate. The biology of uveal melanoma is different to cutaneous melanoma. *BRAF* mutations are uncommon and overall uveal melanoma appears to have a less complex genetic profile, without an ultraviolet radiation DNA damage signature and with a low mutational burden [33]. More than 80% of cases have an activating mutation in *GNAQ* or *GNA11* and these are present from early tumor development, suggesting a pre-dominant role in driving uveal melanoma [83]. These mutations lead to constitutive activation of signaling pathways, including the RAS-RAF-MEK-ERK pathway. Another commonly found mutation is inactivation of *BAP1*, which is highly expressed in metastasizing tumors, suggesting a role in tumor progression [84]. In order to better assess the prognosis of these patients we need to integrate clinical and histopathological data with tumor mutation analysis and gene expression profiles. There is no systemic adjuvant treatment that effectively reduces the risk of metastases [85], and once these develop, the median OS is poor (between 3 and 12 months) with no proven standard of care treatment [86]. As described above, *BRAF* inhibitors are ineffective in uveal melanoma. Checkpoint inhibitors also appear to have little activity, with ORR of 3%, stable disease greater than 6 months observed in four patients (7%) and median OS of 9.5 months (95% CI: 5.5–15 months) in a retrospective analysis of 58 patients treated with PD-1/PDL-1 inhibitors across nine cancer centers [38].

Uveal melanoma is a rare disease and most of the evidence after decades of chemotherapy-based approaches comes from heterogeneous sources, comprised mainly of retrospective studies, single-arm trials and subset analysis in unselected metastatic melanoma trials. Chemotherapy has been used widely with different regimens including dacarbazine, temozolomide, fotemustine, gemcitabine, cisplatin, treosulfan and vincristine. Unfortunately the results have always been disappointing, with very low ORR and inconsistent reports on PFS and OS [87]. A published review of literature on systemic treatments for uveal melanoma from 1980

to 2013 revealed an ORR for either single or combination chemotherapy of around 4% [88]. Biochemotherapy has been assessed in four small Phase II trials using combination chemotherapy plus IFN- α /IL-2, and showed an ORR of 10%, although again this varied considerably between trials [88].

As the RAS-RAF-MEK-ERK pathway is usually constitutively activated in uveal melanomas, several trials have compared targeted agents with chemotherapy in this patient group. The SUAVE trial randomized patients to either sunitinib or dacarbazine, but the results were disappointing, with ORR of 0 versus 8% respectively, and no improvement in PFS or OS with sunitinib [89]. Selumetinib was assessed in a randomized Phase II trial compared with chemotherapy (temozolomide or dacarbazine), with a higher ORR (14 vs 0%) and improved PFS (15.9 vs 7 weeks; HR: 0.46; $p < 0.001$) yet no significant improvement in OS [34]. In the SUMIT trial, a Phase III randomized trial of dacarbazine plus selumetinib versus dacarbazine plus placebo ORR was poor in both arms (3.1 vs 0%; $p = 0.36$) and there was no significant difference in the primary end-point of PFS (2.8 vs 1.8 months, respectively; HR: 0.78; $p = 0.32$) [35]. The SELPAC trial is ongoing to assess the role of selumetinib with or without paclitaxel (EudraCT: 2014-004437-22).

Finally, due to the high incidence of liver metastases and commonly liver-only disease, many local approaches with chemotherapy have been investigated. The use of arterial chemo-embolization appears to be moderately effective according to uncontrolled studies [90]. Hepatic intra-arterial infusion with fotemustine was recently compared with an intravenous arm in an EORTC randomized Phase III trial [91]. Despite the higher ORR (10.5 vs 2.4%) and PFS (4.5 vs 3.5 months; HR: 0.62; $p = 0.002$), it did not translate into an improved OS [91]. Another randomized Phase III trial with intrahepatic melphalan versus best available treatment reported a higher ORR (34 vs 2%; $p < 0.001$) and PFS (8.2 vs 1.6 months; $p < 0.001$) for the experimental arm, but no OS benefit, perhaps due to the high cross-over (55%) [92]. Overall, regional treatments with chemotherapy may have a role in selected patients with liver-only disease, until more effective systemic treatments are identified [90].

Conclusion & future perspective

Single-agent chemotherapy has little activity in advanced cutaneous melanoma and no proven survival benefit, although responses are seen in a minority of patients. Despite decades of trials, a systematic review of 41 trials showed that combination chemotherapy can be associated with a higher objective response rate (ORR), but is also often more toxic, with no demonstrable survival benefit [68]. A meta-analysis of the use of biochemotherapy similarly showed that, despite increasing ORR, there is no improved survival benefit [66]. Chemotherapy has largely been superseded by the use of immune checkpoint inhibitors and, in *BRAF* mutant melanoma, by combination *BRAF*/MEK inhibitor treatment, at least as first- and/or second-line treatment for advanced melanoma. However, chemotherapy could still play an important role in the armamentarium against melanoma.

One such role may be as second- or third-line treatment, after the failure of immunotherapy and, where appropriate, targeted therapy. Patients without a targetable mutation in particular potentially have only one line of treatment available besides chemotherapy, or trials of experimental agents, if treated upfront with combination CTLA-4/PD-1 inhibitor treatment, or are intolerant of immunotherapy. There is evidence that chemotherapy can provide clinical benefit in patients who have progressed on immunotherapy treatment. In a large Phase II trial comparing pembrolizumab with investigator-choice chemotherapy (ICC) in patients who had progressed post-ipilimumab treatment, the chemotherapies used (dacarbazine, temozolomide, carboplatin, paclitaxel or carboplatin plus paclitaxel) produced a combined ORR of only 4%, but a moderate disease control rate (DCR) of 22% [93]. A similar Phase III study of nivolumab versus ICC (dacarbazine or carboplatin plus paclitaxel) in patients who had progressed on ipilimumab found an ORR of 11% to ICC (all responses being seen in patients treated with carboplatin plus paclitaxel, rather than dacarbazine), with a DCR of 45% [94]. For both studies, in addition to previous ipilimumab treatment, about 50% of patients had received a previous line of chemotherapy as well. Thus the potential role chemotherapy can play in managing patients for whom immunotherapy is no longer an option should not be forgotten.

Also, as outlined above, subtypes of melanoma such as mucosal and uveal melanoma

are less responsive to immunotherapy and usually do not contain targetable somatic mutations. For mucosal melanoma patients chemotherapy remains a reasonable treatment option to consider, preferably combined with novel agents as part of a clinical trial. For uveal melanoma patients, intrahepatic chemotherapy may result in disease control, but has no clear impact on overall survival (OS). Newer chemotherapy agents continue to fail to live up to early promises of increased efficacy as single agents, but further research into mechanisms of resistance to systemic treatment will enable novel combination regimens to be explored. DNA damage response mechanisms and dysregulation of the apoptotic pathway are clear mechanisms of resistance to chemotherapy treatment, with mutations in the tumor suppressor gene TP53 commonly occurring in both *BRAF* wild-type and *BRAF* mutant melanoma [95]. The combination of traditional DNA damaging chemotherapy with novel cell cycle checkpoint inhibitors, including ATM and ATR inhibitors, represents just one of many exciting new combination treatment approaches to explore in the next few years [96]. Detailed genomic analysis of tumor samples and circulating tumor DNA (ctDNA), along with the development of novel preclinical models, including patient-derived xenografts (PDXs) and circulating tumor cell-derived xenografts (CDXs) is greatly increasing our understanding of the genomic complexity of melanoma, with the potential to better explore mechanisms of resistance to treatment and novel therapeutic approaches [97]. While the outlook for advanced melanoma has significantly improved in the past decade, it remains one of the most aggressive and difficult to treat cancers, which will continue to require a multimodality approach in the years to come.

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