Advances in melanoma treatment?

E. Seront, J.-F. Baurain

Melanoma is one of the cancers with the fastest growing incidence. The main reason for that is the greater sun exposure of pale Caucasian resulting from a profound lifestyle modification. Melanoma has also a bad reputation of a rapid killer. This is due to the lack of efficacious treatment in advanced disease. We have to bear in mind that early stages are curable. Therefore, public education is mandatory for early detection. Nowadays, the current staging of early stage melanoma includes a sentinel lymph node biopsy. More than half of the patients with a lymph node invaded will relapse within 5 years. No adjuvant therapy may prevent these relapses. IFN-α could only delay the onset of relapses while patients are under treatment. There are some elements suggesting that those who benefit the most of this treatment are those with an ulcerated primary tumor. The standard treatment for advanced or metastatic disease remains DTIC as single agent with limited efficacy. However, we are at the dawn of a new era in the treatment of melanoma. Mutations in genes encoding proteins involved in signal transduction such as bRAF have been identified. Inhibitors of these proteins have been developed and tested in clinic with astonishing efficacy. Hope is also coming with new antibodies blocking CTLA-4, which is powerful break of T-cell. Large randomized trials with all these agents are ongoing. Within 10 years, the treatment of our patients will change with specific treatment for each subtype of melanoma.

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Introduction

Melanoma is the most fatal form of skin cancer. While it accounts for only 4% of all skin cancer, it is responsible for more than 77% of deaths from skin cancer. The incidence of melanoma, 7% of cancers in developed countries, is rising at a rate greater than any other human cancer. In 1935, the lifetime risk of an American developing melanoma was 1 in 1,500, while it is nowadays 1 in 68 individuals.[1-3] The main reason for this increasing incidence is greater exposure of pale Caucasian skin to ultraviolets, resulting from modifications of our lifestyle during these last decades (inexpensive flights to warmer climates and sunny countries, bikinis, solarium,…). At present, the highest worldwide incidences are observed in Australia and New Zealand. In Europe, the highest incidence rates are found in Switzerland, Norway, Sweden, and Denmark.

If incidence of melanoma is still increasing, the overall mortality rate has remained stable during the last decades. This could reflect the improvement in public education to screening methods, leading to diagnosis at an earlier stage. Indeed more than 90% of early stage melanoma is cured with surgery alone. Identification of high-risk patients may still improve the rate of early diagnosis.

Nowadays, survival is limited in advanced disease due to the lack of efficient treatment. We will briefly

Authors: dr. Emmanuel Seront, dr. Jean-Francois Baurain, Department of Medical Oncology, Cliniques Universitaires Saint-Luc, Brussels, Belgium.
Please send all correspondence to: J.-F. Baurain, Cliniques universitaires Saint-Luc, Department of Medical Oncology, Brussels, Belgium, tel: 0032 2 764 54 73, e-mail: jean-francois.baurain@uclouvain.be

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review the different melanoma treatments existing to prevent relapse and for treatment of advanced disease. Then, we will focus on innovative treatments in the prevention of the relapse and the treatment of the disease, such as tumor vaccines and targeted therapies.

Environmental and genetic risk factors

Early diagnosis is the key in melanoma management. Awareness of melanoma risk factors is therefore important. These factors are environmental and genetic. The main environmental risk factor is well known. Intense even if intermittent sun exposure, particularly during childhood, is a significant risk factor for melanoma. In addition, cumulative UV exposure over the years may also contribute. Accordingly, the International Agency for Research on Cancer (IARC) has recently recognized that sun bed use is linked to an increased melanoma incidence. Our sun exposure has also increased with the cheaper flights to sun exposed holiday resorts throughout the year. These 2 factors may explain the greater incidence observed over the last decades.[4-6]

Genetic factors contribute to melanoma development since 10% of melanoma arises in families. Familial malignant melanoma is usually an autosomal dominant trait and the main responsible gene is *Cyclin Dependent Kinase Inhibitor 2A (CDKN2A)*, located on chromosome 9p21 region. *CDKN2A* encodes the tumor suppressor protein p16 (INK4a).[7-9] The risk for developing a melanoma in carriers of mutated *CDKN2A* is 30% at 50 years and 67% at 80 years. But only 20% of families with a predisposition to melanoma have germ-line mutations in gene *CDKN2A*, indicating the involvement of other genes. One of them is *CDK4*, coding for a cyclin-dependent kinase involved in cell cycle regulation.[10] Another is *Melanocortin 1 Receptor (MC1R)* which encodes a G-protein coupled membrane receptor present on melanocytes and melanoma cells. Gene *MC1R* is very polymorphic, with >65 non-synonymous alleles identified to date.[11] Families with any of these mutated alleles should be closely and regularly followed by dermatologists.

Importance of a correct staging

Melanoma staging is an important step, as it determines the clinical outcome and therefore the treatment. The risks of recurrence of and death from melanoma are closely related to the stage at presentation. The most critical determinants of prognosis are the thickness of the primary melanoma, or Breslow's index, the ulceration of the primary tumor, and the regional lymph node status.[12]

The very early stage of disease (stage I to IIA) is characterized by a localized tumor that is either <4 mm in thickness without ulceration or <2 mm in thickness with ulceration. These patients are curable with surgery in 70-90% of cases. Patients with melanomas that are thicker than 4 mm have an approximately 50% risk of relapse, and those with lymph node involvement have a 50-85% risk of metastasis depending on the number of invaded nodes. For these patients an adjuvant treatment is mandatory, but still lacking at the moment.

For patients presenting with a metastatic disease, survival is poor. Here the important prognostic factors are the localization of the metastases (cutaneous, lymph node versus lung or visceral as liver or bone) and the plasma level of LDH. Palliative chemotherapy is the most common therapy, but new treatments become available through clinical studies.

Adjuvant treatment in early stage melanoma

Disappointing as it is, neither chemotherapy nor radiotherapy or tumor vaccines have a demonstrated clinical activity as adjuvant treatment in melanoma patients at early stages after resection of the primary tumor. The only adjuvant treatment that is approved by the US Food and Drug Administration is interferon-alpha (IFN-α), a cytokine that is produced by leucocytes in response to a viral infection. IFN-α might have a direct growth inhibitory effect on the melanoma cells, as well as an antiangiogenic activity. Moreover, several investigators propose that IFN-α has an effect on host cells, rather than tumor cells, leading to improved immune responses.

These recommendations for high dose of IFN-α are derived from 2 American randomized studies (Eastern Cooperative Oncology Group (ECOG) 1684, ECOG 1690) comparing IFN-α to a placebo or a tumor

vaccine in melanoma patients with stage IIB and III. In study ECOG 1684, there was a statistically significant improvement of disease-free survival (DFS) at 5 years: 37% versus 26%.[13] However, the improvement in overall survival (OS) at 5 years was not significant: 46% versus 37%. The study ECOG 1690 confirms these results.[14] However, other trials performed in the US with high or moderate IFN-α doses failed to confirm these results. A meta-analysis of all these trials, comparing IFN-α at any dose to placebo, showed a significantly lower rate of relapse (hazard ratio (HR) 0,83, 95% confidence interval (CI) 0,77-0,90) and a statistically non significant lower rate of mortality (HR 0,93, 95% CI 0,85-1,02). It indicated a clear dose response effect with a longer relapse free survival at higher doses, without impact on OS.[15]

In Europe, the 2 largest studies with IFN-α were conducted by the EORTC in stage III melanoma patients. The first study compared placebo with a moderate dose of IFN-α for 1 or 2 years (EORTC 18952). It failed to demonstrate any clinical benefit.[16] This was confirmed in the second study (EORTC 18991) comparing placebo to a pegylated form of IFN-α for 5 years.[17] In a retrospective exploratory analysis, a clinical benefit in OS was seen in patients without lymph node metastasis at diagnosis and in those having an ulcerated primary tumor.[18] Therefore, the EORTC has decided to launch a large multicentre study where patients without lymph node involvement and an ulcerated primary tumor will be randomized between pegylated IFN-α and observation.

One drawback of IFN-α is its important toxicity profile. Multiple signs of autoimmunity are present in 15-30% of the treated patients, and they include thyroid dysfunction, vitiligo, and apparition of auto-antibodies. Autoimmunity symptoms could reflect the anti-tumor efficacy of IFN-α: Gogas reported that autoimmunity following IFN-α was associated with an improved clinical outcome, both in terms of DFS and OS.[19] But this has not been confirmed in other studies and there is currently no appropriate methodology to detect autoantibodies in IFN-α-treated patients as a surrogate marker for clinical efficacy.[20,21]

So nowadays, there is no data for supporting the use of IFN-α as standard adjuvant treatment in melanoma patients. Therefore, patients should preferably be included in one of the large adjuvant clinical trials ongoing.

Systemic treatment in metastatic melanoma

Patients with a metastatic melanoma have a median survival time of 6-12 months and a 3-year survival rate of 10%. Patients with distant metastases require systemic therapy, even though no such treatment has demonstrated a significant effect on survival.

Chemotherapy

Advanced melanoma is poorly chemosensitive and no randomized trial demonstrated the superiority of chemotherapy over observation and supportive care. Response to single agent chemotherapy is observed in only 8-20% of patients and complete response is rare (<3%). Median survival associated with chemotherapy is only 9 months, suggesting a limited impact on survival.[22,23] An antitumor effect was shown for few agents including alkylating drugs (dacarbazine, temozolomide), platinum analogs, nitrosourea and tubular toxins.

Dacarbazine, also called DTIC, is generally considered the standard agent in metastatic melanoma, although no trial compared dacarbazine with observation. This is possibly due to its favorable toxicity profile with only minor nausea and vomiting. Temozolomide is a dacarbazine analog. Unlike dacarbazine, it can be taken orally, does not require metabolic activation and crosses the blood-brain barrier. Its clinical efficacy was found to be similar to that of dacarbazine in a phase III trial. Response rate was similar (13,5 versus 12,1%), median progression-free survival (PFS) was not improved (1.9 versus 1.5 months), neither was median survival (7.7 versus 6.4 months).[24]

Fotemustine is a nitrosourea that crosses the blood-brain barrier. It was compared to DTIC in a randomized trial for metastatic melanoma with or without brain metastasis. Although the response rate was twice higher with fotemustine (15 versus 7%, p=0.043), the median time to progression (1.9 versus 1.8 months) and median survival (7.3 versus 5.6 months) were not significantly different. Patients treated with fotemustine had a lower risk to develop brain metastasis (18 versus 23%) with a longer median

time to brain metastasis development (22.7 versus 7.2 months). Hematologic toxicity is however greater, with grade 3 to 4 neutropenia (51% with fotemustine versus 5% with DTIC) and thrombocytopenia (43% versus 6%).[25] In Belgium, fotemustine is now reimbursed for metastatic melanoma patients without brain metastasis.

Agents acting on microtubules such as taxanes have demonstrated only modest activity with a response rate below 15%.[26] Platinum compounds are rarely used in monotherapy but sometimes in combination with DTIC or vinblastine. The advantage of such combinations in melanoma remains unproven. Although the response rate may appear increased (30-50%), large prospective trials of a combination versus dacarbazine or temozolomide alone have not confirmed any bonus in PFS or OS. In addition, combination is associated with an increased toxicity.[27-29] This strategy should therefore be kept for particular cases, for example when a rapid response is needed because of a critically progressing disease.

Immunotherapy

More than one century ago, scientists started to envision that our immune system could clear us from our tumors. This possibility was based initially on the resounding successes of the first bacterial and viral vaccines, and later on important observations in animal models. In humans, melanoma was considered to be a good case for the development of immunotherapy, because spontaneous remissions of metastases can be observed and could possibly result from an immune attack. Current strategies include non-specific immune stimuli such as cytokines, or vaccines containing tumor-specific antigens.

Cytokines have been extensively studied in melanoma, with disappointing results. IFN-α used as a single agent or in combination with chemotherapy has not demonstrated any clinical activity, with the exception of the adjuvant setting as indicated above. Interleukin-2 (IL-2) has generated much interest, and in particular for the duration of the response observed in some complete responders. Based on a retrospective analysis of the 8 clinical trials, the overall objective response rate was 16% (6% of complete response and 10% of partial response) with a mean duration of 8.9 months (range 4 to 106 months). Fifty-nine percent of complete responders remained progression-free at 7 years. Responses were even seen in patients with visceral metastases or large tumor burden.[30] Baseline performance status is an important predictive prognostic factor for response to IL-2. Noteworthy, autoimmune complications such as vitiligo seem to be correlated to a better response.[31,32] But only a limited proportion of patients can benefit from IL-2, ought to severe toxicities: hypotension, cardiac arrhythmia, pulmonary edema, fever, capillary leak syndrome and rarely death. To decrease this toxicity, lower doses have been used but are less effective.

The combination of IL-2 and IFN-α gives a higher response rate than IL-2 alone, but there is no significant difference for the median survival duration.[33] IL-2 has also been given in association with chemotherapy. A meta-analysis of 9 randomized trials of biochemotherapy (IL-2 +/- IFN-α with chemotherapy) showed higher response rates. Objective response ranged from 16-48% for biochemotherapy versus 11-30% for chemotherapy. But none of the trials detected a statistically significant improvement in survival: median survival ranged from 8.4 to 12 months for biochemotherapy and from 8.7 to 15.8 months for chemotherapy. In all the trials, a greater toxicity was reported for the biochemotherapy arm.[34] This type of biochemotherapy is therefore not recommended for melanoma patients.

Two other interleukins, IL-15 and IL-21, are currently investigated as single drugs. Preliminary results suggest that they are biologically active and well tolerated.[35-37]

Human tumor cells bear at their surface antigens that can be recognized by autologous T cells. This antigenicity leads to the development of therapeutic anticancer vaccines that should induce tumor regressions or prevent the development of cancer.. Over the last decade, numerous small clinical trials have been performed in melanoma patients with different tumor-specific antigens and different vaccine modalities (peptides, proteins, dendritic cells, or recombinant viruses). No major toxicity has been associated with these vaccines.[38-41] A few tumor regressions were observed and overall less than 5% of the patients presented with a partial or complete tumor response. However, in these patients responses were long lasting. Detailed immunological analysis

Table 1. New targeted therapies for melanoma treatment.

Type of drug tested		Type of study performed and results			
Class	**Name**	**Regimen**	**Type**	**Indication**	**Results**
signal transduction inhibitors					
BRAF	sorafenib	alone	phase II	second line	OR+SD=19%
		with CT[a]	phase II	second line	OR=24%
		with CT[b]	phase III	second line	no efficacy
		with CT[a]	phase III	first line	ongoing
	PLK4032	alone	phase II	second line	OR=60%
MEK	AZD6244	alone	phase II	first line	OR=5%
HSP-90	KOS-593	alone	phase II	second line	ongoing
antiangiogenesis					
VEGF	bevacizumab	with CT[b]	phase II	second line	OR=17%
			phase III	second line	ongoing
	axitinib	alone	phase II		ongoing
antiapoptotic					
Bcl-2	oblimersen	with CT[a]	phase III	first line	no efficacy
oxidative stress	STA-4783	with CT[c]	phase II	first line	OR=15%
			phase III	first line	no efficacy
immunotherapy					
Anti-CTLA-4	tremelimumab	alone	phase III	first line	no efficacy
	ipilimumab	alone	phase II	second line	OR=20%
		alone	phase III	adjuvant	ongoing
		with CTa	phase III	first line	results pending
ASCI	MAGE-A3	alone	phase II	first line	OR=7%
		alone	phase III	adjuvant	ongoing
		with CTa	phase II	first line	ongoing

CT=chemotherapy, OR=overall response rate, SD=stable disease, regimen used in combination with chemotherapy: [a]=dacarbazine, [b]=carboplatine + paclitaxel, [c]=paclitaxel.

of some of vaccinated patients showed strong anti-tumor T cell responses. Amplified autologous anti-tumor lymphocytes have been adoptively transferred after a lymphocyte depleting chemotherapy in metastatic melanoma patients. The overall response was around 40% with also mixed responses, meaning some tumors regressed while others are progressing. All this suggests that the main limiting factor for clinical efficacy is a phenomenon of resistance of the tumor to T lymphocyte attack.[42] Current research programs aim at elucidating the mechanisms of this resistance and to develop new vaccination strategies that circumvent this roadblock. One may combine tumor vaccines or also called antigen specific cancer immunotherapeutics (ASCI) with immunomodulators. The other is to vaccinate high-risk stage III patients after a curative surgery. In the currently running DERMA trial, patients with resected macroscopically positive lymph nodes are randomized between MAGE-A3 ASCI and a placebo.

Novel therapies

Like the other tumors, melanoma derives from dysregulations in specific signaling pathways that are potential targets for drug therapy. Currently, the 3 targets in clinical development are the *BRAF* activating mutations, the overexpression of *BCL2*, and the pro-

duction of angiogenic factors. New targets are in the pipeline, such as the *PTEN* mutations present in 30% of melanomas, the amplification of *AKT3* found in 40-60% of melanomas, the inactivating mutations of tumor suppressor gene *CDKN2A*, or the activating mutations of gene *CDK4* present in familial melanomas. Noteworthy, 75-80% of melanoma harbor a mutation in RAF/RAS/MEK pathway, implicated in proliferation and resistance to apoptosis. Finally, new immunomodulators such as the inhibitors of CTLA-4 generated promising results (*Table 1* on page 50).

Therapies targeting signal transduction

BRAF is a serine threonine kinase of the RAF/RAS/MEK pathway. It is the most frequently mutated oncogene identified to date in melanoma, present in 60-70% of cases.[43] Immediately upstream of BRAF is NRAS, which is mutated and constitutively activated in another 15% of melanomas.[44] Sorafenib is a small multikinase inhibitor that selectively blocks BRAF, c-RAS, VEGFR-2, VEGFR-3, PDGFR and c-KIT. As a single-agent sorafenib has been credited of objective responses and stabilization of the disease in 19% of stage IV melanoma.[45] More tumor regressions were observed when sorafenib was added to chemotherapy. In a phase II trial, 101 metastatic melanoma patients received dacarbazine with or without sorafenib (2 x 400 mg/d). The addition of sorafenib improved the median PFS (21.1 versus 11.7 weeks, p=0.068) and the objective response rate (24 versus 12%). However, no difference in median OS was observed (51.3 versus 45.6 weeks). The regimen was well tolerated and had a manageable toxicity profile.[46] Similarly, encouraging results were reported in a phase II trial with sorafenib combined to temozolomide.[47] In second line treatment of advanced melanoma, a recent randomized phase III placebo-controlled study did not show a benefit to the association of sorafenib to carboplatin taxol: it did not improve PFS or response rate.[48] However, the efficacy of this combination remains to be determined in chemotherapy-naïve advanced melanoma patients. Such a trial is currently ongoing (intergroup trial E2603). One can conclude that the combinatorial efficacy of sorafenib seems to vary from one chemotherapeutic drug to another, and that the optimal partner remains to be identified.

RAS mutations being found in approximately 15% of melanoma, inhibiting the NRAS pathway is a potential treatment. The only clinical agents used to date to inhibit this pathway are the farnesyltransferase inhibitors that impair the posttranslational modification of the RAS proteins and prevent their membrane localization, which is required for signaling activity.[49] These agents have not yet been evaluated in melanoma patients.

New drugs inhibiting the RAF/RAS/MEK pathway are currently in investigation. RAF265 and PLX4032 are 2 BRAF inhibitors studied in early phase II with the promising results of up to 60% response rate.[50,51] AZD 6244 is a specific MEK inhibitor that in phase II trial shows little activity (5% response rate) and no difference in PFS compared with temozolomide.[52] KOS-953 is an inhibitor of heat shock protein 90 and targets proteins that are chaperoned by Hsp90 such as RAF and Akt. This drug is now in phase II trials and results are expected soon.[53]

Mutations of Akt and mTOR pathways are also found in melanoma. New molecules targeting those pathways could have a potential benefit for melanoma patient. These drugs are tested in small phase II studies.

Antiangiogenesis treatment

Development of melanoma depends on angiogenesis, stimulated by the binding of VEGF to its receptor on the cell surface. Bevacizumab is a humanized anti-VEGF monoclonal antibody that shows efficacy in colorectal cancer. A phase II trial evaluated the combination of bevacizumab, paclitaxel and carboplatine in melanoma patients. The combination was well tolerated and clinically active: response rate reached 17%, 57% of these clinical responders had a stable disease for at least 8 weeks, and median PFS and OS times were 6 and 12 months, respectively.[54] A phase III is currently underway. Axitinib is an orally active inhibitor of VEGFR-1,-2 and -3, PDGFR, and c-kit, which is being evaluated in advanced melanoma.[55]

Newer therapies targeting integrin are under exploration. Volociximab is a chimeric monoclonal antibody recognizing and inhibiting the integrin $\alpha 5\beta 1$. Etaracizumab is a humanized monoclonal antibody targeting the integrin $\alpha 5\beta 3$. These integrins mediate

the attachment of endothelial cells to fibronectin present in the extracellular matrix, an important step in angiogenesis. These two drugs need further trials to confirm their efficacy discovered in phase I studies.

Antiapoptotic agents

Bcl-2 is an antiapoptotic protein that regulates the mitochondrial or intrincic apoptotic pathway and is overexpressed in melanoma cells, contributing to resistance to chemotherapy.[56,57] Oblimersen is an antisense DNA molecule that inhibits the production of Bcl-2. It is used in combination with chemotherapy, with the rationale that by shutting off Bcl-2 it will push the cancer cells to undergo apoptosis when exposed to a DNA-damaging agent, such as dacarbazine, that will trigger the intrinsic apoptosis pathway. A phase I trial of oblimersen and DTIC demonstrated a 15-47% decrease of Bcl-2, which could increase the chemosensibility. A randomized phase III trial compared DTIC with and without oblimersen in 771 patients with previously untreated melanoma. Adding oblimersen slightly improved the median survival at 24-month minimum follow-up (9.0 versus months; $p=0.077$) and significantly increased the median PFS time (2.6 versus 1.6 months; $p<0.001$), the overall response rate (13.5% versus 7.5%; $p=0.0007$), the complete response rate (2.8% versus 0.8%), and the durable response rate (7.3% versus 3.6%; $p=0.03$). OS was significantly prolonged only in patients with a normal serum LDH.[58] Other studies are currently ongoing to confirm this benefice. Other compounds, such as ABT-737 or ABT-263, are mimicking the natural agonists Bcl-2 and are in earlier phases of clinical development.[59,60]

Oxidative stress inducers are a new class of anticancer drugs. One of them is the synthetic compound STA-4783, which increases the amount of reactive oxygen species in tumor cells apparently through an upregulation of the heat shock protein HSP70. This drug was combined to paclitaxel in a phase II that has shown an increase of response rate and prolonged PFS. A randomized phase II study by O'Day et al. enrolled 81 patients to a combination of STA-4783 and paclitaxel versus paclitaxel alone. The ORR was 15% in the combination arm and 3% in the paclitaxel arm, thereby confirming the potential benefit of the combination.[61] Therefore, a randomized phase III clinical trial was launched but prematurely stopped. The data safety committee board observed a greater mortality rate in the combination arm.

New developments in immunotherapy

One major limiting factor for clinical efficacy in immunotherapy appears to be local immunosuppression in the tumor microenvironment. Melanoma was shown to inhibit T cell activation through different mechanisms such as secretion of immunosuppressive cytokines or local depletion in amino acids. One possibility to circumvent this roadblock is to lower the threshold of T cell activation. This threshold is regulated in part by the expression at the surface of the T cells of receptors that, when engaged by their ligands present on antigen-presenting cells, will inhibit activation of the cell. These inhibitory receptors can be viewed as natural breaks built in the immune system. Two receptors of that kind have been studied extensively: CTLA-4 (cytotoxic T lymphocyte antigen-4) and PD-1 (programmed death-1).[62] CTLA-4 blockade with monoclonal antibodies enhanced antitumor T cell immunity in animals.[63]

Tremelimumab is a human monoclonal IgG2 anti-CTLA-4 antibody with a serum half-life of 22 days. Phase I and II trials have shown clinical efficacy in patients with advanced melanoma with a median survival of 10.3 months (at 10 mg/kg monthly) and 11 months (at 15 mg/kg every 3 months), and a duration of response from 183-540 days).[64,65] In patients with advanced relapsed or refractory melanoma tremelimumab has been compared in a randomised phase III study with dacarbazine or temozolomide. This study failed to show the benefit of tremelilumab in OS as first-line treatment of patients with metastatic melanoma when compared with standard chemotherapy; median OS of 11.8 months versus 10.7 months.[66] In patients with metastatic melanoma the combination of tremilinumab and high dose interferon has shown, in a phase II trial, a response rate of 19%, with acceptable toxicities.[67]

Ipilimumab is a human monoclonal IgG1 anti-CTLA-4 antibody. Phase I and II clinical trials in patients with metastatic melanoma have demonstrated promising effects on tumor progression, with objective response rates of approximately 20% and sustained

responses in some patients receiving ipilimumab as monotherapy.[68] The most commonly reported adverse events are diarrhea, pruritus, dermatitis and fatigue, and are generally easily manageable. But sometimes severe autoimmune reactions have been observed such as hypophysitis or thyroiditis. In a phase II trial, 72 untreated advanced patients were randomized between ipilimumab alone or with dacarbazine and showed that patients receiving the combination can achieve a little bit longer OS (386 days) and approximately 10% of patients were alive after 2 years follow up.[69] We are waiting the results of a large phase III study in patients with advanced or relapsed melanoma that received dacarbazine alone or in combination with ipilimumab. Finally, ipilimumab is also tested by the EORTC in a randomized phase III trial (ipilimumab versus observation) for high-risk melanoma patients after complete resection of macroscopically positive lymph nodes.

Conclusion

Melanoma treatment remains a major challenge. Early detection, through insistent prevention campaigns, and accurate staging are keys to ensure the best possible prognosis. Stage III melanoma remains associated with up to 60% of metastatic relapse and ultimate death due to melanoma. New adjuvant treatments are under study with as objective to change this bad prognosis. They are based on the stimulation of the patient's immune system with anti-tumor vaccines (MAGE-A3 vaccine) or anti-CTLA-4 antibodies. In metastatic patients, single agent chemotherapy remains the gold standard, but it has a limited efficacy. Therefore, the best option for many of these patients is to be included in one of the several studies investigating new promising agents.

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Key messages for clinical practice

Intermittent sun exposure remains the most important risk factor for melanoma development, especially in children. Very early stage melanomas are curable. Therefore, correct staging including lymph node assessment is mandatory. No active adjuvant treatment exists. First-line treatment of advanced or metastatic melanoma remains DTIC in monotherapy with limited activity. But we are at the dawn of a new era and new-targeted therapies are coming. These new agents target unique mutations found in certain subtypes of melanoma. Other agents counteract immunotolerance by unlocking T-lymphocytes recognizing melanoma cells. Today more than ever, it is key to include all melanoma patients in clinical trials evaluating these new drugs.

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