L'Institut Servier Annual Scientific Sessions

19th Colloquium 2019
Revolutions in cancer treatment:
how can they be integrated?

Melanomas

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Abstract

The incidence of melanoma has shown a constant increase since the 1980s. Surgery is the standard of care for localised disease. Melanomas have a high metastatic potential and the prognosis of advanced melanoma was, until recently, very grim. Since 2011, improved understanding of the molecular mechanisms of melanoma and cancer immunology have led to two new treatment strategies: immunotherapy (which is presented in this article) and targeted therapies. Overall median survival is now reaching 3 years or more, and some patients can hope for a cure. Unfortunately, even these agents are not completely effective, and a lot of work is underway to identify predictive biomarkers and evaluate different combinations to improve response rates. These agents have also been shown to be effective as adjuvant therapy in melanomas with a high risk of recurrence, and marketing authorisations have recently been issued for these.

The incidence of melanoma has been increasing by about 10% per year for the past 50 years. In 2017, there were 15,404 new cases and 1,783 deaths from melanoma in France, with a median age at diagnosis of 60 years (source: INCa). Surgical treatment is usually curative for localised, operable disease. Melanoma, however, has a high metastatic potential and the prognosis for patients with metastatic melanoma has, until recently, been very poor. For more than 30 years, the standard of care for advanced stage disease was chemotherapy using dacarbazine, with response rates of 5% to 15% and median survival of only 6 to 9 months.

Since 2012, a revolution has taken place in the treatment of metastatic melanoma as a result of significant improvements in the understanding of the molecular mechanisms behind melanoma and the immunology of cancer. Two new treatment strategies are now available: immunotherapy (with immune checkpoint inhibitors [ICPs]), which are presented in this article, and targeted therapies (BRAF and MEK inhibitors) for patients with a BRAF V600 mutation.

ANTI-CTLA-4 ANTIBODIES

The first ICP was ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[1] CTLA-4 inhibits the initial phase of T-lymphocyte stimulation within secondary lymphoid organs. Ipilimumab blocks this negative signal thereby stimulating development of immunity against the tumour. This is the first drug that has been found to improve survival for patients with stage 4 melanoma.[2] The objective response rate was only 10%, but overall survival was significantly improved with 45% of patients alive at 1 year, compared with 30% on previous treatments. Long-term survival curves showed a plateau, with about 20% of the patients still alive 3 years after starting treatment, suggesting that a patient who is still alive after 3 years will remain so.[3, 4] A marketing authorisation (MA) was issued for ipilimumab in 2011.

New unconventional response profiles have been described with immunotherapy,[5, 6] such as pseudoprogression, which appears at the beginning of treatment due to tumour infiltration of immune cells. It is important to be aware of this phenomenon, even though it only occurs in <10% of patients, to avoid incorrectly concluding that the treatment is not effective. Physicians are also becoming familiar with the new forms of immunological toxicity associated with the mechanisms of action of these drugs. These mainly affect the skin or the gastrointestinal tract (particularly forms of inflammatory colitis similar to Crohn's disease), and sometimes causing hepatitis or endocrine inflammation. Immunological toxicity requires special vigilance to ensure prompt initiation of treatment, which is based on corticosteroids. Ipilimumab has been associated with grade 3 and 4 toxicities in 20% to 30% of patients.[7, 8]

ANTI-PD-1 ANTIBODIES

Ipilimumab was rapidly followed by other ICPs that target programmed cell death protein (PD-1). PD-1 blocks the activation of T-lymphocytes during the effector phase in peripheral tissues. Two anti-PD-1 drugs, nivolumab and pembrolizumab, have been available as first-line treatments for melanoma since 2015, including in patients with BRAF V600 mutation. The response rate of 30% to 40% is higher than with ipilimumab, with 74% survival at 1 year. Both drugs have demonstrated their superiority in terms of overall survival and progression-free survival in phase 3 studies,[9, 10] compared with chemotherapy (dacarbazine) as first-line treatment in the case of nivolumab, or compared with ipilimumab, in the case of pembrolizumab, as both first-line and second-line treatment. PD-1 inhibitors are also better tolerated than ipilimumab, with 10% to 15% of patients developing grade 3 or 4 immunological adverse events.

Updated data at 3 years confirmed the benefits of treatment with nivolumab compared with chemotherapy, with a 3-year survival rate of 51% in the nivolumab group compared with 22% in the dacarbazine group. The response rate with nivolumab was stable (43%) and 20% of patients had a full response. Median survival was 37.5 months (compared with 11 months for chemotherapy).[11] The updated 5-year survival data with pembrolizumab was rate of 39% compared with 31% with ipilimumab, confirming the superiority of pembrolizumab. The response rate with pembrolizumab was 42%, with 14% of patients having complete response, and the median survival was 33 months compared with 16 months on ipilimumab.[8] The median survival for patients treated with first-line pembrolizumab was 39 months.

COMBINATION OF ANTI-PD-1 AND ANTI-CTLA-4

An MA has just been issued for the combination of ipilimumab and nivolumab for the first-line treatment of metastatic melanoma without a *BRAF* V600 mutation. A phase 3 study was published in 2015 comparing nivolumab alone, the combination of ipilimumab + nivolumab, and ipilimumab alone.[12] The data from this study, updated at 5 years, showed that the response rates have remained stable relative to the initial report (58% with the combination of anti-PD-1/anti-CTLA-4, 45% with anti-PD-1 monotherapy and 19% with anti-CTLA-4 monotherapy) but the complete response rates increased (to 22% with the combination of anti-PD-1/anti-CTLA-4, 19% with anti-PD-1 monotherapy and 6% with anti-CTLA-4 monotherapy).[7] The 5-year survival rate of patients treated with the combination of nivolumab + ipilimumab was 52%, 44% with nivolumab monotherapy and 26% with ipilimumab alone. Median survival for the group of patients who were given the combination of nivolumab + ipilimumab could not be calculated because it was longer than 5 years; the median survival for the patients treated with nivolumab monotherapy was 37 months and ipilimumab monotherapy was 20 months.[7] The toxicity of the combination of nivolumab + ipilimumab was high, with a 60% incidence of grade 3/4 toxicities. The MA for this combination was issued in France in 2016; reimbursement is limited to first-line treatment in patients with no BRAF mutations and no active brain metastases.

ADJUVANT TREATMENTS

Currently available adjuvant treatments are intended for patients with stage 3 melanoma, i.e. those with lymph node involvement and/or regional metastases, treated with surgery. These patients have a lower probability of survival (69% at 10 years) than patients with stage 1 (95%) or 2 (84%) melanoma.[13]

Ipilimumab is the first ICP to have shown a benefit in overall survival as an adjuvant therapy, with a 5-year survival rate of 65% versus 54% for placebo.[14] Treatment duration is 3 years and the dose of 10 mg/kg is higher than is used for metastatic melanoma (3 mg/kg), resulting in considerable toxicity (including 5 deaths due to toxicity in a group of 495 patients), which limits its use in the adjuvant setting. It has been approved by the Food and Drug Administration (FDA) since 2015, but it is not available in Europe for this indication.

A study has shown benefit in terms of recurrence-free survival (70.5% versus 60.8%) for nivolumab in comparison with ipilimumab for the adjuvant treatment of stage 3 (and stage 4 after surgery) melanoma for 1 year, with much more acceptable toxicity (10% versus 43% of patients on nivolumab versus ipilimumab discontinuing due to toxicity). Overall survival data are not yet available because the follow-up period is still too short.[15] Nivolumab received an MA as adjuvant therapy in 2018.

Pembrolizumab has demonstrated efficacy compared with placebo for the same indication over 1 year. Compared with placebo, pembrolizumab reduced the risk of recurrence or death by 43%, with a tolerability profile similar to previous data (14% incidence of grade 3 or 4 adverse events). Not enough time has elapsed to obtain data on overall survival.[16] An MA was also issued for adjuvant pembrolizumab in 2018.

NEOADJUVANT TREATMENTS

Neoadjuvant immunotherapy has been investigated for patients with operable stage 3 melanoma in phase 1 and 2 trials, with different designs and aims, in relatively small cohorts of patients.[17-20] The protocol for neoadjuvant treatment is not yet well defined. The OpACIN-neo study[20] examined the combination of an anti-PD-1 (nivolumab) and an anti-CTLA-4 (ipilimumab) at low doses to limit toxicity, for 6 to 8 weeks, followed by surgical excision (limited to affected lymph nodes), thus permitting histological evaluation. A pathological complete response (pCR), i.e. the absence of tumour cells in the lymph nodes, could be a promising marker for future therapeutic trials, since in this study the patients with a pCR after neoadjuvant treatment had no further recurrences.[20]

The value of neoadjuvant treatment for patients with operable stage 3 melanoma may be i) to reduce the size of the tumour, ii) to facilitate surgery, iii) to improve locoregional control and possibly survival, and iv) to permit clinical pathology checking in addition to clinical and radiological checks. Large-scale trials are being established to investigate the role of neoadjuvant treatment.

CONCLUSION

Patients with metastatic melanoma may now benefit from immunotherapy with anti-PD-1s, making it possible to achieve a median survival of 3 years with acceptable tolerability. The combination of anti-PD-1 and anti-CTLA-4 agents can result in a median survival of more than 5 years, but at the cost of non-negligible levels of toxicity. We still do not have biomarkers to predict the efficacy and toxicity for these treatments. Adjuvant treatment with anti-PD-1s is beginning to be prescribed, with improvements in progression-free survival and possibly overall survival expected. Neoadjuvant treatments seem very promising based on data from phase 1 and 2 studies, but their superiority to adjuvant treatments still needs to be confirmed in phase 3 studies.

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