BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

DETICENE, DACARBAZINE LIPOMED, DACARBAZINE MEDAC (dacarbazine), alkylating agent

No clinical benefit demonstrated in the next-line treatment of advanced melanoma after failure of immunotherapies and/or therapies targeted at B-RAF mutations.

Insufficient actual benefit in other situations, especially in first–line treatment, due to the role of immunotherapy and therapies targeting B-RAF mutations.

Main points

- Before the availability of immunotherapy and so-called targeted therapies in 2012, dacarbazine was commonly used as a first-line treatment for advanced melanoma, despite the absence of any demonstrated effect on survival.
- Immunotherapy and anti-BRAF therapies alone or in combination with anti-MEK agents have supplanted dacarbazine due to the demonstration of a superior efficacy in terms of disease-free survival and/or overall survival.
- Cytotoxic agents, including dacarbazine, are now a last-line treatment.

Pre-existing indications

Proprietary medicinal products based on dacarbazine are also indicated in the treatment of Hodgkin’s lymphoma and soft tissue sarcomas in adults.

Therapeutic use

The current management of advanced (unresectable or metastatic) melanoma involves screening patients for a BRAF mutation in the tumour as soon as they are diagnosed:

- In the absence of BRAF mutation, immunotherapies such as nivolumab (OPDIVO) or pembrolizumab (KEYTRUDA) are recommended as first-line treatment. The combination of ipilimumab with nivolumab is an option only for patients having ECOG 0 or 1 and no active cerebral metastase. In second-line treatment ipilimumab (anti-CTL4, YERVOY) is a therapeutic option although there are no data on its efficacy after progression on anti-PD1 agents. In the event of failure, chemotherapy, including dacarbazine, is discussed as third-line treatment. Depending on the patient’s characteristics and the apparent toxicities on immunotherapy, the use of dacarbazine may also be discussed from the second line as an alternative to ipilimumab.
- If there is BRAFB-RAF mutation, the first-line treatment consists of a dual therapy targeting this mutation (combination of a BRAF inhibitor and an anti-MEK agent): dabrafenib (TAFINLAR) combined with trametinib (MEKINIST) or vemurafenib (ZELBORAF) combined with cobimetinib (COTELLIC). In some cases, the use of anti-PD1 immunotherapy may be proposed. Nivolumab (OPDIVO) or pembrolizumab (KEYTRUDA) are recommended as second-line treatment after dual therapy failure. Ipilimumab (YERVOY) may be proposed as third-line treatment. Chemotherapy, including dacarbazine, is discussed as a fourth-line treatment. Depending on the patient’s characteristics and the apparent toxicities on immunotherapy, the use of dacarbazine may also be discussed as a third-line treatment as an alternative to ipilimumab.

* This summary does not cover these indications.

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Role of the proprietary medicinal product in the therapeutic strategy
Since the arrival of immunotherapy and so-called targeted therapies, chemotherapy, including dacarbazine, no longer has a role in the first-line treatment of advanced-stage melanoma. According to the patient’s general condition, dacarbazine retains a limited role in the next-line treatment of advanced melanoma in:
- second or third line after failure of immunotherapy, in the absence of B-RAF mutation;
- third or fourth line after failure of dual therapy with anti-B-RAF and anti-MEK agents, and then of immunotherapy in the case of B-RAF mutation.
Depending on the patient’s profile, notably in patients in poor general condition and having comorbidities and/or high LDH, recourse to support care alone must be discussed at this stage of treatment.

Clinical data
- The available clinical data no longer reflect current practice and therefore do not permit assessment of the benefit and/or therapeutic contribution of dacarbazine after failure of immunotherapy and/or so-called targeted therapies.
- As with other alkylating agents, dacarbazine toxicity is mainly haematological (myelosuppression) and digestive (nausea and vomiting). Hepatobiliary disorders have also been reported. More rarely, renal toxicity may occur later than for other alkylating agents (around 21 days) and toxicity on the central nervous system with seizures and dementia has been reported with high doses of dacarbazine.

Special prescribing conditions
- Hospital prescription, with prescription restricted to cancer treatment, haematology and clinical oncology specialists and departments.
- Medicine requiring special monitoring during treatment

Benefit of the medicinal product
- The actual benefit* of dacarbazine in the treatment of advanced-stage melanoma is:
  - moderate as next-line treatment after failure of immunotherapies and/or so-called targeted therapies, depending on B-RAF status,
  - insufficient for reimbursement by National Health Insurance in the other situations, notably as a first-line treatment.
- Dacarbazine does not provide clinical added value** (CAV V) in the treatment of advanced-stage melanoma with regard to the evolution of the therapeutic strategy and in the absence of clinical data in the event of failure of immunotherapies and/or so-called targeted therapies, depending on B-RAF status.
- Recommends maintenance on the list of reimbursable products for hospital use as the next-line treatment for advanced-stage melanoma and does not recommend maintenance on the list of reimbursable products for hospital use in the other situations, especially as a first-line treatment.

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement of the medicinal product for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV (equivalent to “no CAV”) means “no clinical added value”.