Second Malignant Neoplasm Occurring Years After Hyperthermic Isolated Limb Perfusion for Melanoma

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Background: Hyperthermic isolated limb perfusion (HILP) is a useful therapeutic option in patients with locally advanced melanoma of the extremities. Because HILP allows very high doses of cytotoxic agents to be administered without systemic leakage, the theoretical risk of a secondary malignant neoplasm is real, particularly in the treated limb. Such an event has never been reported to our knowledge, however, possibly in part because survival in these patients is often too short to permit the development of chemically induced cancers.

Observations: We describe 2 cases of secondary rare cancers in 2 elderly women: 1 fatal pleomorphic sarcoma and 1 Merkel cell carcinoma, which developed on the same limb 16 years after HILP for melanoma. The first patient had an exceptional prolonged complete response after HILP for unresectable regional metastases, while the second had been overtreated with HILP and dacarbazine in an adjuvant setting for an early-stage melanoma.

Conclusions: Because long-term survivors of regionally advanced melanoma, although rare, do exist, candidates for HILP should be warned of the risk of long-term development of nonmelanoma secondary cancers. The risk-benefit balance of high-dose local chemotherapy should be carefully evaluated in the light of these findings, especially in patients with early-stage melanoma or other non–life-threatening medical conditions.

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HYPERHEARTMIC ISOLATED
limb perfusion (HILP), a
form of regional chemo-
therapy used since the
1950s, is effective as a pal-
liative procedure in patients with locally
advanced, unresectable malignant melanoma
of a limb and has been used in other region-
ally advanced neoplasms such as soft-tissue sarcoma and Merkel cell carcinoma. It consists of surgically isolating the affected extremity by vessel cannulation to perfuse chemotherapy in mild hyperthermia conditions (ie, limb temperature, 38°C-40°C). Because systemic leakage of the drug is prevented by applying a tourniquet at the root of the limb, very high concentrations—up to 30-fold the level tolerated in systemic infusion—can be administered without causing excessive toxic effects. Because melphalan, the main antiproliferative drug used in HILP, is a known dose-dependent carcinogen, the theoretical risk of secondary cancer is real. Herein, we describe the first 2 cases (to our knowledge) of secondary cancer occurring years after HILP for malignant melanoma.

REPORT OF A CASE

CASE 1
A 49-year-old woman was diagnosed as having malignant melanoma on her left leg in 1968. A large resection of the lesion was performed, along with chemotherapy, and the patient experienced a long period of remission, which was frequently interrupted by episodes of in-transit cutaneous metastasis that were treated by iterative excisions. In 1988, she had multiple cutaneous metastases on her left leg that were too numerous for serial excisions. She refused the suggested amputation of her leg. The use of HILP with melphalan was then proposed and accepted. The outcome was excellent: the patient subsequently experienced a 16-year period of complete remission.

In 2004, at the age of 85 years, she presented with a nonpigmented fast-growing tumor on the external side of her left leg (Figure 1). The findings of histologic examination of a biopsy specimen were suggestive of an undifferentiated neoplasm. Immunohistochemical stains were negative for S-100 protein, HMB-45, and B-cell– and T-cell–associated antigens and positive for CD68. A diagnosis of myeloid sarcoma was suspected, and radiotherapy (4900 rad [to convert to grays, multiply by 0.01]) was administered, without any effect. A large surgical resection, followed by a graft, was then performed. Histologic examination of the entire piece confirmed the final diagnosis of high-grade pleomorphic sarcoma with local rhabdoid differentiation (Figure 2).
Further evolution was marked by a local recurrence, followed in a few months by rapidly fatal lung metastases despite amputation of the patient’s left leg.

CASE 2

A 57-year-old woman presented with a pigmented lesion on her left leg in 1991. Excision and histologic examination revealed a nodular malignant melanoma with a Breslow thickness of 1.4 mm. The patient underwent intensive adjuvant therapy consisting of prophylactic radical lymph node dissection of the left inguinal area, HILP with melphalan, and systemic chemotherapy with dacarbazine (10 cycles). She then experienced a 16-year period of complete remission and was assessed by regular clinical monitoring.

She presented in April 2008, at the age of 73 years, with a purple nodule measuring 1 cm in diameter on the external side of her left leg. There was no apparent lymphedema. Histologic examination of a biopsy specimen showed features of a typical Merkel cell carcinoma, and immunostains were positive for cytokeratin 20. A large excision along with a sentinel node biopsy did not show any lymph node involvement. Adjuvant local radiotherapy was then administered to the tumor site.

In May 2009, the patient presented with 3 palpable subcutaneous nodules measuring 1 to 4 cm in diameter on her left leg (Figure 3), distributed both above and below the previous tumor. Because the clinical diagnosis was considered uncertain, a biopsy specimen was obtained from each nodule. The findings of histologic examination of the specimens were consistent with a deeply invasive Merkel cell carcinoma (Figure 4). Because there were no distant metastases, a surgical resection, followed by another local radiotherapy regimen, was planned.

COMMENT

We report 2 exceptional cases of nonmelanoma skin cancers (ie, pleomorphic sarcoma and Merkel cell carcinoma) that developed 16 years after HILP for malignant melanoma. These malignant neoplasms are not known to be associated with malignant melanoma, and their location on the same limb where the procedure had been performed was highly suggestive of a causal role of HILP in their oncogenesis. Also, the clinical presentation in case 2, which was characterized by a very small primary lesion followed 1 year later by multiple subcutaneous nodules, some of which were located 20 cm below the primary lesion, is compatible with multifocal chemo-induced primary tumors as well as with metastases of the previous tumor. In both patients, high doses of melphalan had been used.
Melphalan, a derivative of nitrogen mustard, is a di-alkylating agent that is widely used to treat various cancers and other medical conditions and is also known as a potent carcinogenic drug. It exerts an antiproliferative effect by cross-linking the DNA double-helix strands, impairing the DNA replication, and leading to apoptosis. Beyond its ability to induce lymphosarcoma, lung tumors, and peritoneal sarcomas after peritoneal injection in murine models, melphalan has been shown to dramatically increase the relative risk of acute nonlymphocytic leukemia developing in patients who have been treated for ovarian cancer, breast cancer, or multiple myeloma, and this risk increases with increasing doses. Furthermore, secondary sarcomas have already been described in childhood cancer survivors who were treated with high doses of alkylating agents.

To our knowledge, the occurrence of secondary malignant neoplasms after HILP with melphalan has never been reported. This is not surprising, as (1) HILP is rather an infrequent treatment and is restricted to tertiary care centers; (2) little data are available about long-term (ie, >10 years) follow-up of patients after HILP; and (3) since the publication more than 10 years ago of a large controlled trial that showed no benefit of prophylactic HILP after complete resection of localized (high-risk) melanoma, most patients treated with HILP had American Joint Committee on Cancer stage III (or even stage IV) disease with unresectable regional limb metastases and therefore a life expectancy that is probably too short for later events such as secondary cancers to occur. In our report, the duration of 16 years after HILP in both patients was remarkably long: patient 1 had an unexpected response to therapy and an exceptional survival considering the staging of her melanoma when the procedure was performed (American Joint Committee on Cancer stage IIIB), whereas patient 2 had undoubtedly been overtreated according to the current French guidelines for the management of nonmetastatic melanoma, and this risk increases with increasing doses. Furthermore, secondary sarcomas have already been described in childhood cancer survivors who were treated with high doses of alkylating agents.

In contrast with other cancers in which secondary malignant tumors have emerged as a major concern because of the prolonged survival that can be observed after the administration of very efficient but carcinogenic chemotherapies, such a risk is rarely considered in patients with melanoma. In view of our observations and previous studies, HILP should definitely be discontinued in a prophylactic setting, and the benefits and risks of this treatment should be carefully evaluated in other situations. Although rare, long-term survivors of advanced, unresectable stage III or even stage IV melanoma do exist. In a recent population-based study of stage IV melanoma, 10 of 316 patients had a survival time of more than 4 years after the occurrence of distant metastases. Three of the 10 patients finally died of melanoma, and 1 died of chemo-induced leukemia after having received numerous maintenance infusions of alkylating agents. We conclude from such observations that the potential carcinogenic effects of chemotherapies must be considered in melanoma as in other cancers.

Hyperthermic isolated limb perfusion remains a useful therapeutic option in patients with recurring, non-resectable in-transit metastases of limb melanoma, a subgroup of whom will experience prolonged complete remission. However, such patients should be informed of the long-term risk of secondary nonmelanoma skin cancers developing, even decades after treatment. Finally, we are concerned that the use of isolated limb infusion—a less complex, hence more available, alternative to HILP also involving high doses of melphalan—has been recently proposed in the treatment of refractory extensive warts of the extremities. In view of our findings, the risk-benefit balance of such a treatment in nonmalignant conditions should be carefully reassessed.

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REFERENCES