The first patient had an exceptional prolonged coma and 16 years after HILP for 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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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 can-
cers 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, im-
pairing the DNA replication, and leading to apoptosis. Beyond its ability to induce lymphosarcoma, lung tum-
ers, and peritoneal sarcomas after peritoneal injection in
murine models, melphalan has been shown to dra-
matically increase the relative risk of acute nonlympho-
cytic leukemia developing in patients who have been
treated for ovarian cancer, breast cancer, or multiple my-
eloma, and this risk increases with increasing doses.3 Fur-
thermore, secondary sarcomas have already been de-
scribed in childhood cancer survivors who were treated
with high doses of alkylating agents.3

To our knowledge, the occurrence of secondary mal-
gnant 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 cen-
ters; (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 com-
plete resection of localized (high-risk) melanoma,6 most
patients treated with HILP had American Joint Commit-
tee on Cancer stage III (or even stage IV) disease with un-
resectable regional limb metastases and therefore a life ex-
pectancy 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 mela-
noma 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.7 In any case, the long period after treatment with
HILP may have allowed the development of such secondary
tumors.

In contrast with other cancers in which secondary ma-
gnant tumors have emerged as a major concern because
of the prolonged survival that can be observed after the ad-
ministration of very efficient but carcinogenic chemothera-
pies, such a risk is rarely considered in patients with mela-
noma. In view of our observations and previous studies,6
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,8 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 af-
fter having received numerous maintenance infusions of al-
kylation agents. We conclude from such observations that
the potential carcinogenic effects of chemotherapy must
be considered in melanoma as in other cancers.

Hyperthermic isolated limb perfusion remains a use-
ful therapeutic option in patients with recurring, non-
reseetable in-transit metastases of limb melanoma, a sub-
group of whom will experience prolonged complete remission.9 However, such patients should be informed
of the long-term risk of secondary nonmelanoma skin can-
cers developing, even decades after treatment. Finally,
we are concerned that the use of isolated limb infu-
sion—a less complex, hence more available, alternative
to HILP also involving high doses of melphalan—has been
recently proposed in the treatment of refractory exten-
sive warts of the extremities.10 In view of our findings,
the risk–benefit balance of such a treatment in nonma-
lignant conditions should be carefully reassessed.

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