Isolated Limb Perfusion for Unresectable Melanoma of the Extremities

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Hypothesis: In patients with truly unresectable melanoma of the extremities, results after isolated limb perfusion (ILP) are absent in the literature. Complete response rates are probably lower than the reported 54% for locoregional recurrent melanoma. In these patients, ILP with melphalan and tumor necrosis factor α (TNF-α) could be superior to ILP with melphalan alone.

Design: Retrospective analysis with a median follow-up period of 21 months (interquartile range, 9-40 months).

Setting: Two tertiary care cancer centers in the Netherlands.

Patients: We assessed all 130 consecutive patients who underwent ILP for unresectable melanoma of the extremities, performed between 1978 and 2001. Of these patients, 38% had stage IIIA melanoma and 45% had stage IIIB melanoma according to criteria of the MD Anderson Cancer Center. Lesions were considered unresectable on the basis of their size, number, or localization.

Interventions: Forty ILPs were performed with melphalan, and 90 were done with TNF-α and melphalan.

Main Outcome Measures: Response rate, disease-free survival, limb salvage rate, and overall survival.

Results: In 45% of the patients, a complete response was attained after ILP with melphalan (95% confidence interval, 29%-61%) compared with 59% after ILP with TNF-α and melphalan (95% confidence interval, 49%-69%; P=.14). The time to complete response was 3 months (interquartile range, 2-6 months) vs 2 months (interquartile range, 1-3 months; P=.01), respectively. The recurrence rate and median limb recurrence-free survival were not significantly different for both ILP types. The overall limb salvage rate was 96%. Overall 5-year survival was 29% (95% confidence interval, 20%-38%). The ILP type was not an independent prognostic factor for complete response, nor was limb recurrence-free survival, whereas stage IIIA was a favorable prognostic factor (P=.01 and P=.02, respectively). Favorable prognostic factors for improved survival were complete response (P<.001) and a tumor size of 3 cm or less (P=.01).

Conclusions: In more than half of the patients with truly unresectable melanoma of the extremities, a complete response was obtained after ILP with melphalan with or without TNF-α. The ILP type was not an independent prognostic factor for complete response, limb recurrence-free survival, or overall survival.

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applied around the limb, proximal to the region of ILP. After insertion of the catheters, the isolated limb is perfused with extracorporeal circulation, oxygenated, and propelled by a heart-lung machine. A melphalan dose of 13 mg/L for the upper limb and 10 mg/L for the lower limb is added to the perfusate. For TNF-α this is 3 mg and 4 mg, respectively, irrespective of limb volume. In 11 patients who received TM-ILP, 0.2 mg of interferon gamma was added and was injected subcutaneously for 2 days before surgery. The same dose was given intraoperatively and injected into the perfusate. During ILP, adequate tissue temperatures are achieved and maintained by heating the heparinized perfusate and applying a warm-water blanket around the limb. Limb temperatures are kept between 37°C and 38°C (normothermia) for M-ILP or 38°C and 40°C (mild hyperthermia) for TM-ILP; M-ILP lasts 1 hour, and TM-ILP lasts 90 minutes. At the termination of ILP, the perfusate is drained out and the limb is rinsed with an electrolyte solution. The tourniquet is then released, and the catheters are removed. In 71 patients (55%), a regional lymph node dissection had already been done before ILP or was performed during ILP.

Regional toxicity after ILP was graded according to the method of Wierbink et al.10

Tumor response was measured by World Health Organization criteria.14 Postoperatively, patients stayed in bed with the leg elevated until acute toxic reactions of the limb subsided. Patients were gradually mobilized with the help of a physiotherapist and discharged when fully ambulatory. Long-term morbidity was routinely scored by identifying the following signs and symptoms: edema, venous thrombosis, arterial thrombosis, nerve injury, muscle atrophy or fibrosis, recurrent erysipelas, and subjective complaints of pain and malfunction of the perfused limb. All items were scored until 2 years after ILP. The median duration of follow-up was 21 months (range, 2 days to 17 years).

Statistical analysis was performed with the t test when comparing groups with a normal distribution or with the Mann-Whitney test, were used if the distribution of data was not normal. For limb recurrence-free survival, Kaplan-Meier analysis was performed and a log-rank test was used for the comparison of differences between independent groups. Significance was set at P≤.05.

### RESULTS

**TUMOR RESPONSE**

Tumor response after ILP is displayed in Table 2. A complete response was attained following 72 (55%) of 130 ILPs at a median of 2 months after the procedure. The median duration of a complete response was 10 months (interquartile range, 5-25 months). A partial

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### Table 1. Population Characteristics: Stage of Disease*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristic</th>
<th>Patients, No. (%):</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Primary melanoma</td>
<td>1 (1)</td>
</tr>
<tr>
<td>II A</td>
<td>Local recurrence</td>
<td>4 (3)</td>
</tr>
<tr>
<td>II B</td>
<td>Satellites</td>
<td>5 (4)</td>
</tr>
<tr>
<td>II A</td>
<td>In-transit metastases</td>
<td>50 (38)</td>
</tr>
<tr>
<td>II B</td>
<td>Regional node metastases</td>
<td>21 (2)</td>
</tr>
<tr>
<td>II AB</td>
<td>In-transit and regional</td>
<td>59 (45)</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
<td>9 (7)</td>
</tr>
</tbody>
</table>

*Adapted for stage II according to criteria of the MD Anderson Cancer Center (Houston, Tex).

†One patient had a local recurrence (5 cm × 5 cm) on the sole of the foot and regional lymph node metastases. The other patient had a large primary melanoma (9 cm × 9 cm) on the lower limb and regional lymph node metastases.

### Table 2. Complete Response, Time to Complete Response, Recurrence Rate, and Limb Recurrence–free Survival in Unresectable Melanoma of the Extremities

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete Response, No. (%)</th>
<th>95% CI, %</th>
<th>Value</th>
<th>Time to Complete Response, mo*</th>
<th>Recurrence Rate, No. (%)</th>
<th>95% CI, %</th>
<th>Value</th>
<th>Limb Recurrence–free Survival, mo</th>
<th>95% CI, %</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-ILP (n = 40)</td>
<td>18 (45)</td>
<td>29-61</td>
<td></td>
<td>3 (2-6)</td>
<td>10 (56)</td>
<td>30-81</td>
<td></td>
<td>30</td>
<td>0-60</td>
<td></td>
</tr>
<tr>
<td>TM-ILP (n = 90)</td>
<td>53 (59)</td>
<td>49-69</td>
<td>.14</td>
<td>2 (1-3)</td>
<td>26 (48)</td>
<td>34-62</td>
<td>.60</td>
<td>16</td>
<td>9-23</td>
<td>.70</td>
</tr>
<tr>
<td>Overall (N=130)</td>
<td>72 (56)</td>
<td>46-63</td>
<td></td>
<td>2 (1-4)</td>
<td>36 (50)</td>
<td>39-63</td>
<td></td>
<td>18</td>
<td>11-25</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; M-ILP, isolated limb perfusion with melphalan; TM-ILP, isolated limb perfusion with tumor necrosis factor α and melphalan.

*Data are presented as median values with interquartile range (between 25% and 75%) in parentheses, unless otherwise indicated.

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response was obtained after 28 ILPs (22%; 95% confidence interval [CI], 15%-30%), and 6 of these patients were rendered locoregionally disease-free after additional resection of the lesions. Of the patients with a complete response, 36 (50%; 95% CI, 39%-63%) had a recurrence at a median of 6 months after ILP (interquartile range, 3-13 months). The median duration of follow-up in those without recurrence was 21 months (interquartile range, 6-50 months). Median limb recurrence–free survival was 18 months. As indicated in Table 2, there were no significant differences regarding complete response rate, limb recurrence rate, and limb recurrence–free survival between the 2 ILP types. The median time to complete response was significantly different between M-ILP and TM-ILP: 3 months and 2 months, respectively (P = .01).

The results for patients with a high tumor load according to the criteria of Fraker et al (n = 105) were not significantly different from the results of the whole patient population. In these patients, ILP resulted in a complete response in 54 cases (52%; 95% CI, 42%-61%), attained after a median of 2 months (interquartile range, 1-4 months). The complete response rate after M-ILP was 41% (95% CI, 24%-59%), which was not significantly lower than the 58% (95% CI, 45%-68%) attained after TM-ILP (P = .11). The time to complete response was significantly shorter after TM-ILP compared with M-ILP: 2 months (interquartile range, 1-4 months) and 3 months (interquartile range, 2-7 months), respectively (P = .03). Median limb recurrence–free survival after M-ILP was 30 months (95% CI, 3-58 months), which was not significantly different from the 16 months (95% CI, 9-23 months) after TM-ILP (P = .64).

A significantly better effect of TM-ILP on bulky lesions as opposed to multiple small lesions could not be demonstrated. The complete response rate after both TM-ILP and M-ILP in patients with a few lesions larger than 5 cm (n = 18) was 50%. In those with more than 15 lesions of 5 cm or less (n = 65), the complete response rate was 59% (95% CI, 44%-73%) after TM-ILP compared with 37% after M-ILP (95% CI, 13%-61%; P = .11).

**PROGNOSTIC FACTORS FOR COMPLETE RESPONSE AND LIMB RECURRENCE–FREE SURVIVAL**

We performed regression analyses for predictors of complete response and limb recurrence–free survival, for which the following parameters were tested: sex, Breslow thickness and ulceration of the primary tumor, number of previous episodes of excisional surgery on the same limb, site of indicator lesions (eg, arm, thigh, or lower leg), tumor load (high or low according to the criteria of Fraker et al), stage of disease according to the MD Anderson Cancer Center, and ILP type (M-ILP vs TM-ILP). Multivariable logistic regression analysis indicated that the absence of lymph node metastases (stage IIA disease) appeared to be the single independent prognostic factor for complete response, with an odds ratio of 3.5 (95% CI, 1.34-9.43; P = .01). In a Cox regression analysis, MD Anderson stage IIA melanoma also proved to be the strongest predictive factor for limb recurrence–free survival, with an odds ratio of 0.3 (95% CI, 0.12-0.83; P = .02).

### Table 3. Treatment of Limb Relapse or Persistent Lesions After ILP*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete Response With Limb Relapse (n = 36)</th>
<th>Persistent Lesions (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excision</td>
<td>16 (44)</td>
<td>15 (26)</td>
</tr>
<tr>
<td>Radiotherapy and local hyperthermia (with or without excision)</td>
<td>3 (8)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Repeated ILP (with or without excision)</td>
<td>6 (17)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Limb amputation</td>
<td>1 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Chemotherapy or immunotherapy</td>
<td>7 (20)†</td>
<td>15 (26)‡</td>
</tr>
<tr>
<td>None</td>
<td>3 (8)§</td>
<td>16 (28)∥</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage).
†Three patients also underwent excision of lesions, 1 radiation therapy with local hyperthermia, and 1 repeated ILP.
‡Three patients also underwent excision of lesions, 2 radiation therapy with local hyperthermia.
§No additional therapy was given because of progressive distant metastases.
∥Fourteen patients underwent no additional therapy because of progressive distant metastases; 1 patient had complications after ILP with subsequent death, and 1 died of myocardial infarction 2 days after ILP.

**TREATMENT OF RECURRENCE AND PERSISTING LESIONS AFTER ILP**

Data regarding follow-up after ILP are displayed in Table 3, in which the treatment of limb recurrence and persistent lesions is specified. In 4 patients, the limb was amputated during follow-up. After a complete response, 1 patient had a persistent wound infection with extensive infected necrotic soft tissues; 3 months after ILP, exarticulation at the hip joint was inevitable. Another patient underwent an above-knee amputation because of intractable recurrence 18 months after a complete response. Two other patients had persistent lesions after ILP; in one, an amputation of the lower leg was performed 3 months after ILP, and the other underwent an above-knee amputation 14 months later. The last patient was initially treated with radiation therapy for these lesions but developed radiation-induced necrosis. After a median follow-up period of 21 months, the limb salvage rate for all 108 patients was 96%.

**METASTASES AND SURVIVAL**

Table 4 depicts the development of regional node and distant metastases in relation to response after ILP. Distant metastases developed in 72% of the patients who relapsed locoregionally after a complete response, significantly more than the 47% in those without relapse. Median survival was not significantly different between these groups.

The overall 5-year survival of all patients was 29% (95% CI, 20%-38%). Median survival was 25 months. In a Cox regression analysis, the following variables for survival were tested for their independent prognostic value: sex, age, MD Anderson stage of disease, Breslow...
thickness and ulceration of the primary tumor, tumor size of 3 cm or less or larger than 3 cm, high or low tumor load (according to the criteria of Fraker et al9), ILP type, and response (complete or not complete) to ILP. A stepwise backward analysis identified complete response and tumor size of 3 cm or less as independent prognostic factors for a better survival rate, with odds ratios of 0.3 (95% CI, 0.18-0.55; P<.001) and 2.0 (95% CI, 1.16-3.53; P=.01), respectively. In the Figure, survival curves are displayed separately for patients who attained a complete response with ILP compared with those without a complete response. Survival was significantly different between these groups, with a median survival of 44 months (95% CI, 30-57 months) and 15 months (95% CI, 11-19 months), respectively (P<.001). The median survival of 43 months in patients who relapsed after a complete response was also significantly longer compared with the rate of 15 months in those without a complete response (P<.001).

TOXICITY AND MORBIDITY

Table 5 lists the results regarding acute regional toxicity, long-term morbidity, and length of hospital stay. There was no significant difference in any of these outcomes for the 2 ILP types.

Locally unresectable melanoma of the extremities is a major therapeutic problem; few treatment options remain, and the prognosis is unclear and probably limited. Radiation therapy with or without hyperthermia results in an overall response rate of 80%, with the best response in tumors smaller than 4 cm. The disadvantages are that it cannot be applied to large areas of disease and that it has no effect on micrometastatic disease in the rest of the extremity.3 Traditionally, ILP has been considered the treatment of choice for patients with truly unresectable melanoma lesions limited to the extremity. However, the results of ILP in this particular patient group are lacking, with most series presenting data in mixed groups of patients with varying numbers of tumor nodules. The definition of unresectability is not generally agreed on and seems to be subject to the personal assessment of the surgeon. In this series, most of the lesions (81%) were judged to represent high tumor burden according to the criteria of Fraker et al.9 In a few patients (10%), lesions were unresectable based on other criteria such as localization, lesions with unclear margins and/or an inflammatory component, widespread lesions not permitting multiple excisions, or previous carbon dioxide laser ablation.
Our analysis is retrospective with its known pitfalls. Nevertheless, it is a large series based on a well-maintained database, which is to our knowledge the best currently available data set to study the results of ILP in this patient population. To date, there have been no prospective studies on the use of ILP in patients with locally unresectable limb melanoma.

Overall, 55% of our patients attained a complete response after ILP, with 36 patients (28%) cured locoregionally by a single ILP procedure for the rest of the follow-up period of 21 months. The 45% complete response rate after M-ILP in our patients with unresectable melanoma is somewhat lower than the mean 54% complete response rate seen after M-ILP in patients with lesions varying in resectability.15 This can be explained by the difference in tumor load; it has been shown that tumor load, in terms of the number of lesions, total tumor surface area, and nodal status, is an important prognostic factor for tumor response after ILP.10,11,16 However, our complete response rate of 45% after M-ILP is remarkably higher than the 19% complete response rate after M-ILP that was previously reported by Fraker et al17 in a similar subgroup of patients with a high tumor burden. The reason for this difference is unknown, with our 59% complete response rate after TM-ILP being similar to their rate of 58%. Complete response rates after TM-ILP in populations with varying disease burden varied from 64% to 90%,7,9,17–21 probably due to a generally lower tumor load in these studies.

In this analysis, the difference in complete response rates after M-ILP compared with TM-ILP was not statistically significant, although a tendency for a higher response rate after TM-ILP was apparent. This tendency was also shown in the multicenter European phase 2 trial that randomized patients with measurable disease to either TM-ILP or TM-ILP with interferon gamma and compared them with a historical control group treated with M-ILP.18 In that study, a 52% complete response rate after M-ILP and a 73% complete response rate after TM-ILP with interferon gamma were observed. The time to complete response in our series was significantly shorter after TM-ILP compared with M-ILP. Although it was only a 1-month difference, this confirms what was observed in the European trial, in which the difference was 61 vs 225 days.19 In that study, limb recurrence–free survival for patients with a complete response was 15 months after TM-ILP with interferon gamma compared with 19 months after M-ILP, which in our series was 16 and 30 months, respectively. These results suggest that TM-ILP leads to a faster achievement of complete response than M-ILP but that TM-ILP has no additional positive effect on long-term locoregional control in those who attain a complete response. Lejeune22 suggested that large and well-vascularized tumors are particularly sensitive to TNF-α because it acts on their newly formed vessels, with the melphanal treating micrometastatic disease present in the limb. However, the complete response rates for both large and small lesions were similar after M-ILP and TM-ILP in this series.

The single prognostic factor for attaining a complete response was stage IIIA melanoma. That the chance of a complete response is higher in the absence of nodal involvement confirms what has been found in previous studies.10,11,16 Subsequent limb recurrence–free survival was significantly influenced by the presence of nodal metastases. In our high–tumor burden group, the number of lesions did not have prognostic value for attaining a complete response,10,11,16 in contrast to other studies with more mixed stages of disease.

There was no significant difference in acute regional toxicity, long-term morbidity, or length of hospital stay between the 2 ILP types. It has previously been shown that neither TNF-α nor mild hyperthermia (as applied in TM-ILP) increases acute regional toxicity or morbidity compared with M-ILP in normothermic conditions.23–25

Recurrence after ILP was treated with simple local modalities in 70% of the patients. Unfortunately, 4 patients needed an amputation of the limb. Considering that all patients had truly unresectable tumors from the start, the limb salvage rate of 96% is impressive.

The overall 5-year survival in this series was 29%, which is in the lower part of the 26% to 46% range, typical for patients with in-transit metastases with or without lymph node involvement.26 This is assumed to be due to the selection of patients with more extensive disease in this series. Complete response, with or without relapse, and relatively small tumors were favorable prognostic factors for survival. Tumor size proved to be of independent prognostic value in other studies as well, with larger tumors having a worse prognosis.27,28 The significant difference in the occurrence of distant metastatic disease between patients with a complete response who did not relapse locoregionally compared with those with relapse is probably a reflection of the more aggressive nature of disease in the latter group.

As in many other studies of ILP for melanoma, most patients with locoregionally recurrent limb melanoma are women.17,19,25,29,30 This probably results from different biological characteristics of tumors in women as compared with men, although no evidence is available to support this hypothesis.

In conclusion, after a single ILP procedure for locoregionally unresectable melanoma, 55% of patients attain a complete response. Half of these patients are rendered disease-free for a long time. Patients with a complete response have a 3- to 4-fold increase in overall survival compared with those without a complete response. Maximum efforts should be made to obtain a complete response, although the response to ILP is probably partly dictated by the biological features of the disease in the individual patient. This and other studies have found a tendency for a better tumor response after TM-ILP (as compared with M-ILP) in patients with a high tumor burden, which has yet to be proved by ongoing randomized studies.

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