Chapter 3

Isolated Limb Infusion with Melphalan and Actinomycin D for Melanoma: A Systematic Review

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Abstract
Isolated limb infusion (ILI) was developed as a simplified and minimally invasive alternative to isolated limb perfusion (ILP) to treat unresectable limb melanoma. A number of centers around the world have reported their results using this procedure. In this study a systematic review of reported ILI experiences was undertaken. A literature search was conducted according to the guidelines for systematic reviews in order to select eligible papers reporting limb toxicity and response rates following ILI using melphalan and actinomycin D to treat limb melanoma. A total of 576 patients from seven publications were included. Regional toxicity following ILI was low: no visible effect of the treatment or slight erythema or edema was observed in 79% of the patients, while considerable erythema and/or edema with blistering was experienced by 19%. In 2% there was a threatened or actual compartment syndrome. No procedure-related amputation was reported. Complete response occurred in 33% of the patients and partial response in 40%, an overall response rate of 73%. Stable disease and progressive disease were achieved in 14% and 13% of the patients, respectively. This first systematic review of ILI procedures using melphalan and actinomycin D indicates that regional toxicity was generally low, with satisfactory response rates. When comparing ILI and ILP, it must be borne in mind that ILI is often performed in significantly older patients and in patients with higher stages of disease, which decreases the likelihood of a favorable response.
Introduction
Patients who suffer from advanced melanoma confined to a limb are often challenging to treat due to the size and number of the satellite and/or in-transit metastases.\(^1\) Results of systemic therapies have generally been disappointing and although promising results have been reported recently using anti-CTLA4 antibodies and BRAF inhibitors for metastatic melanoma, little is known about the effect of these agents when metastases are limited to a limb.\(^2\) In these patients an isolated limb perfusion (ILP) can be carried out to control the disease and avoid amputation of the disease-bearing limb. Although high response rates have been reported following ILP, the procedure has some major disadvantages.\(^5\) It is invasive and technically complex, requiring a large number of supporting staff including a perfusionist. Furthermore, the procedure is usually considered inappropriate for elderly and frail patients and, finally, a repeat ILP, after recurrence of disease, is often difficult and can result in major complications due to scar tissue from the previous surgical approach to the vessels.\(^6\)–\(^8\)

In the early 1990s the isolated limb infusion (ILI) technique was developed at Melanoma Institute Australia (MIA; formerly known as the Sydney Melanoma Unit) as a simplified and minimally invasive alternative to ILP, with the objective of obtaining the benefits of ILP without incurring its major disadvantages.\(^9\) Since its introduction, the ILI technique has been introduced at many melanoma treatment centers around the world and an increasing number of articles reporting results following the ILI procedure have been published, though often with only limited patient numbers.\(^10\)–\(^13\) Therefore, for the current study we performed the first systematic review of ILI for melanoma using melphalan and actinomycin D in order to describe the combined response rates and limb toxicity profiles.

Detailed descriptions of the preoperative management, technical details of the ILI procedure, and important aspects of post-operative care following ILI are reported elsewhere.\(^14\)–\(^15\)
Methods
The systematic review was conducted according to published guidelines.\textsuperscript{16,17} Using the databases of Medline and Embase we searched the current literature for original articles reporting response rates and toxicity following ILI for melanoma using melphalan and actinomycin D.

For the review we used the search terms: ILI, melanoma, melphalan and actinomycin D. This resulted in 131 possibly eligible papers (Figure 1). After reading the titles and abstracts, reports of ILI using melphalan alone were excluded. Review articles were also excluded as well as case reports, case series describing malignancies other than melanoma without separately reporting the results for melanoma, and papers describing repeat or subsequent procedures. After this first elimination 27 articles reporting response and toxicity following ILI were selected for full text evaluation. Of these papers, 11 were found eligible for the current analysis and an additional three were included after reviewing the reference lists of the full text articles. In order to perform the systematic review, however, not all of these 14 studies could be included since some centers reported their results in more than one paper, for instance both in a single center experience and in a multi-center study, or they reported a follow-up series with additional patients.\textsuperscript{11,18-21} In these cases, we selected the most recent studies that included the largest number of patients in order to prevent duplication of patient results. After taking these criteria into account we were able to include seven studies (two multicenter studies and five single center studies) involving a total of 576 patients in the review.\textsuperscript{12,13,19,20,22-24}
**Figure 1**: Flow diagram outlining the selection process for articles included in the systematic review.
Results

Regional Toxicity Following ILI

All seven publications used the Wieberdink scale to assess the grade of limb toxicity following ILI\textsuperscript{25} (Table 1). The limb toxicity following ILI reported in the seven articles is detailed in Table 2, with the combined results of the systematic review listed in the bottom row.

In this systematic review regional toxicity following ILI was generally low: no visible effect was seen in 33\% of the cases (Grade I), while 46\% of the patients developed slight erythema and/or edema (Grade II). Considerable erythema and/or edema with blistering was seen in 19\% (Grade III). Extensive epidermolysis and/or obvious damage to deep tissues with a threatened or actual compartment syndrome occurred in 2\% of patients (Grade IV). No grade V toxicity (severe tissue damage necessitating amputation) was reported.

Response Rates Following ILI

The reported response rates following ILI for melanoma using melphalan and actinomycin D for the seven studies are shown in Table 3, with the combined results of the systematic review listed in the bottom row. Five studies assessed the response rates according to the handbook for reporting results of cancer treatments published by the World Health Organization (WHO).\textsuperscript{26} This system defines response following treatment as the best clinical outcome from two separate observations more than 4 weeks apart at any time following the procedure. Two studies conducted in the United States, however, assessed the response rates at a single, fixed time point, 3 months following ILI.\textsuperscript{19,23}

Of the 576 patients 33\% experienced a complete response (CR) and 40\% a partial response (PR), an overall response (OR) rate of 73\%. In total 27\% of the patients had a less favorable response to ILI, with stable disease (SD) seen in 14\% and progressive disease (PD) in 13\% of them.
Table 1: Wieberdink toxicity grading.25

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No visible effect</td>
</tr>
<tr>
<td>II</td>
<td>Slight erythema and/or oedema</td>
</tr>
<tr>
<td>III</td>
<td>Considerable erythema and/or oedema with blistering</td>
</tr>
<tr>
<td>IV</td>
<td>Extensive epidermolysis and/or obvious damage to deep tissues with a threatened or actual compartment syndrome</td>
</tr>
<tr>
<td>V</td>
<td>Severe tissue damage necessitating amputation</td>
</tr>
</tbody>
</table>

Table 2: Limb toxicity, assessed using the Wieberdink scale, following ILI for melanoma with melphalan and actinomycin D.12,13,19,20,22-24

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mian, 2001</td>
<td>9</td>
<td>44%</td>
<td>44%</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Kroon, 2008</td>
<td>185</td>
<td>2%</td>
<td>56%</td>
<td>39%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Marsden, 2008</td>
<td>13</td>
<td>0%</td>
<td>46%</td>
<td>38%</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Beasley, 2009</td>
<td>128</td>
<td>64%</td>
<td>35%*</td>
<td>1%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Duprat Neto, 2012</td>
<td>31</td>
<td>0%</td>
<td>40%</td>
<td>50%</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Wong, 2013</td>
<td>79</td>
<td>80%</td>
<td>20%*</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Coventry, 2013</td>
<td>131</td>
<td>27%</td>
<td>60%</td>
<td>11%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>576</strong></td>
<td><strong>33%</strong></td>
<td><strong>46%</strong></td>
<td><strong>19%</strong></td>
<td><strong>2%</strong></td>
<td><strong>0%</strong></td>
</tr>
</tbody>
</table>

*Beasley and Wong reported the combined toxicity for grades II and III

Table 3: Response rates following ILI for melanoma with melphalan and actinomycin D.12,13,19,20,22-24

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients</th>
<th>Response criteria</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mian, 2001</td>
<td>9</td>
<td>best response</td>
<td>44%</td>
<td>56%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Kroon, 2008</td>
<td>185</td>
<td>best response</td>
<td>38%</td>
<td>46%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Marsden, 2008</td>
<td>13</td>
<td>unknown</td>
<td>31%</td>
<td>53%</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>Beasley, 2009</td>
<td>128</td>
<td>3 months</td>
<td>31%</td>
<td>33%</td>
<td>7%</td>
<td>29%</td>
</tr>
<tr>
<td>Duprat Neto, 2012</td>
<td>31</td>
<td>best response</td>
<td>26%</td>
<td>53%</td>
<td>21%</td>
<td>0%</td>
</tr>
<tr>
<td>Wong, 2013</td>
<td>79</td>
<td>3 months</td>
<td>37%</td>
<td>37%</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>Coventry, 2013</td>
<td>131</td>
<td>best response</td>
<td>27%</td>
<td>36%</td>
<td>29%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>576</strong></td>
<td></td>
<td><strong>33%</strong></td>
<td><strong>40%</strong></td>
<td><strong>14%</strong></td>
<td><strong>13%</strong></td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Discussion
Since its introduction in the early 1990s, ILI has become an increasingly applied alternative to the traditionally used ILP technique. Although this first systematic review, including seven eligible studies, showed that side effects following ILI are generally mild or moderate, efforts aimed at reducing limb toxicity are of great interest. A study focusing on toxicity showed that patients with larger limb volumes experience increased toxicity, without receiving higher dosage of cytotoxic drug per liter of tissue. This observation was explained by the rapid melphalan saturation in the limb fat, resulting in relatively more of the cytotoxic agent being available for uptake in muscle and skin, causing more toxicity. With the aim of reducing limb toxicity in these patients Beasley et al. corrected the melphalan dose for ideal body weight (IBW). In their hands this decreased toxicity significantly with only a small decrease in response. However, these results could not be reproduced in a study undertaken at Melanoma Institute Australia in which the ratio between IBW and actual body weight did not predict toxicity or outcome.

In the current systematic review the overall response rate was 73% (CR rate 33%, PR rate 40%). The wide range of response rates (Table 3) is possibly caused by the low number of patients in some of the included studies and the learning curve required to master this new technique. Furthermore, different institutions have used protocols that vary in small but potentially important ways. The impact of these differences in protocol and the effect of increased experience have recently been investigated by Huismans et al., who found that at MIA increased experience and small modifications that were made to the ILI protocol over the years had a positive effect on the outcome. Another explanation for the range in responses could be the time point at which the response to the procedure was assessed. Two of the included studies determined the best response exactly 3 months following the treatment, while most reported the outcome according to the WHO system for reporting responses to treatment, allowing a larger time window to detect the best response.

Despite the differences in experience, protocols and outcome, most investigators have reported that patients who obtain a CR have significantly improved survival compared with non-responders. Achieving a CR can be predicted by several patient-related factors such as stage of disease and limb volume. However, procedure-related factors such as ischemia time, the injection of 30–60mg of papavarine...
into the arterial catheter to maximize vasodilation and raising intra-operative temperatures have also been shown to have a positive effect on response.\textsuperscript{14,15,24} In view of these procedure-related factors, ischemia times at MIA have been increased and peri-operative temperatures have been raised, starting with heating the patient well before the procedure, to increase the initial temperature of the limb, aiming to achieve subcutaneous temperatures in the limb of 38.5–39.0°C at the end of the procedure. Although these measures have resulted in a modest increase in limb toxicity with more Grade III reactions, the procedures have been well tolerated in most cases without lasting side effects, and without causing more Grade IV reactions. The changes are considered to be justified by the increased response rate that has been observed.\textsuperscript{32} Taking this into account, the lower response rates of some studies could in part be caused by the shorter ischemia times or the lower initial limb temperatures, such as were observed in the first phase II trial of ILI.\textsuperscript{10}

Since its introduction in the late 1950s, ILP has been the most frequently used treatment option for locally advanced limb melanoma, with high response rates reported.\textsuperscript{33} A drawback of ILP, however, is the invasive and complex nature of the procedure. During ILP open exposure and cannulation of the femoral or axillary artery and vein is performed to access the limb circulation. The vessels are then connected to an extracorporeal circuit containing a heart-lung machine in order to maintain normal physiological conditions in the isolated limb.\textsuperscript{5,34} A more detailed technical comparison of ILI and ILP, discussing the advantages of the two procedures, is presented in another article in this edition of Seminars in Surgical Oncology.\textsuperscript{15} Despite the disadvantages of the procedure when compared to ILI, ILP for melanoma using melphalan results in CR rates of 40–82% and PR rates of 21–44%.\textsuperscript{35} Although the reported response rates following ILI are generally at the lower end of those reported in published ILP series, it must be borne in mind that most patients treated by ILI are older and have a higher stage of disease than those treated by ILP. This is important since previous reports have shown that both age and stage of disease are prognostic factors for response.\textsuperscript{20,36} Older patients and those with Stage IV disease are often thought to be unsuitable for ILP, while following ILI they do not show any increased toxicity or morbidity;\textsuperscript{20,36} even in patients who have distant metastatic disease, concurrent symptomatic limb disease can effectively be treated by ILI to provide palliative local tumor control and limb salvage.\textsuperscript{37} Finally, ILI provides an ideal treatment...
modality that will allow locoregional treatment to be combined with systemic therapies. For example, a phase I study of ILI using systemic ADH-1 in combination with melphalan achieved a CR rate of 50% and the procedures were well tolerated.

In conclusion, this systematic review of ILI using melphalan and actinomycin D to treat irresectable limb melanoma shows that regional toxicity following the procedure is generally low, and that the procedure results in a satisfactory overall response rate of 73%. This is at the lower end of the spectrum of overall response rates reported after ILP. However, when comparing ILI and ILP it must be recognized that ILI is often used in significantly older patients, and in those suffering with higher stages of disease, which has been shown to decrease the likelihood of a favorable response to regional chemotherapy. To date, no randomized trial directly comparing the outcome of ILP and ILI has been undertaken.
References


