Outcomes of isolated limb perfusion in the treatment of extremity soft tissue sarcoma: A systematic review

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Accepted 17 December 2012
Available online

Abstract

Background: Isolated limb perfusion (ILP) may provide a limb salvage option for locally advanced soft tissue sarcoma (STS) not amenable to local resection.

Methods: A systematic review was performed for studies reporting outcome of ILP for locally advanced STS performed after 1980 in patients aged ≥12 years old. The main endpoints were tumour response and limb salvage rates. Complication and recurrence rates were secondary endpoints.

Results: Eighteen studies were included, providing outcomes for 1030 patients. Tumour necrosis factor-alpha with melphalan was the commonest chemotherapy regime. When reported, 22% of cases achieved a complete tumour response (216/964, 15 studies) with an overall response rate of 72% (660/911, 15 studies). At median follow-up times ranging between 11 and 125 months, the limb salvage rate was 81% in patients who otherwise would have been subjected to amputation. However, 27% of patients suffered local recurrence and 40% suffered distant failure. ILP was associated with severe locoregional reactions in 4% (22/603) of patients. Amputation due to complications within 30 days was necessary in 1.2% of cases (7/586, nine studies). There was insufficient evidence to determine the effect of ILP on survival.

Conclusion: ILP induces a high tumour response rate, leads to a high limb salvage rate but is associated with a high recurrence rate. It provides a limb salvage alternative to amputation when local control is necessary.

Keywords: Isolated limb perfusion; Sarcoma; Soft tissue sarcoma; TNF-α

Introduction

Extremity sarcomas account for less than 1% of all malignancies.1–3 Isolated limb perfusion (ILP) is a treatment for selected patients with locally advanced extremity sarcoma or melanoma in whom local resection would be mutilating and where a high risk of local recurrence exists.4,5 In patients with large and deep-seated soft tissue sarcomas of the extremities, published data indicate that amputation does not increase survival.6,7 The trend has therefore been towards limb preservation in the form of wide local resection with post-operative radiotherapy, at the cost of potentially severe disability in the affected limb. ILP has been used with success in the treatment of advanced melanoma but early attempts for sarcoma met with disappointing results; the technique was abandoned in the 1980s. Interest was re-ignited when Lejeune and colleagues8 added TNF-α to standard treatment protocols based on melphalan and showed limb salvage rates approaching 80%. Subsequently, a multicentred European study of 186 patients with limb sarcoma showed the high tumour response rate and limb salvage rate achieved with TNF-α and melphalan, allowing its approval in European markets.9

During ILP, the limb circulation is isolated from the systemic circulation by applying a tourniquet and cannulating the major vessels. Hyperthermia is induced and chemotherapy drugs are administered through an oxygenated extracorporeal perfusion circuit. Melphalan (L-phenylalanine mustard) and recombinant human tumour necrosis factor-α (TNF-α), used in combination, have become the most popular cytotoxic agents and can be administered at doses

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15–25 times greater than via the systemic route. Definitive local complications associated with ILP are rare but serious, including early amputation and locoregional toxicity from chemotherapy. Systemic leakage of drugs poses a potentially fatal risk, particularly with the use of higher dose TNF-α, leading to the use of lower doses. Since most reports on ILP are based on small patient cohorts, a review of these studies is warranted. Although systematic reviews exist for melanoma and thorough reviews exist for the use of ILP in extremity sarcoma, a formally conducted systematic review focusing solely on sarcoma is lacking. The aim of this paper was to systematically review the efficacy and safety of ILP for extremity sarcoma.

Methods

Study selection

A systematic search of PubMed, the Cochrane Library and the Current Controlled Trials Register was performed for studies reporting the outcomes of isolated limb perfusion for soft tissue sarcomas (STS). Search terms used included “isolated limb perfusion”, “sarcoma”, “soft tissue sarcoma”, “outcomes” and “survival” singly or in combination. The “related articles” function in PubMed was used to broaden the search and a manual search of reference lists in relevant articles was also performed. Studies were limited to those published after 1980 and in the English language. The last search was performed on 12 December 2011.

Inclusion/exclusion criteria

Studies were included on satisfaction of the following criteria: (i) patients had a situation where the tumour was judged to necessitate amputation, with aggressive and poorly differentiated sarcoma; (ii) design was randomised controlled trial (RCT), prospective observational or retrospective cohort study; (iii) provided outcome data on patients undergoing ILP for locally advanced extremity sarcoma; (iv) any temperature and chemotherapy regime; (v) included only patients aged 12 years and older; (vi) where there was overlap in patient cohorts between two studies, the study that contained the more recent and larger cohort was included. Studies with fewer than ten patients undergoing ILP or studies where ILP was employed as an adjunct following local resection were excluded.

Data extraction and study outcomes

Data were extracted independently by two authors. Discrepancies in outcome extraction were resolved by re-examination of the relevant study until consensus was achieved. The main endpoints of this study were tumour response rate and limb salvage rate. Complication rates were a secondary endpoint. Tumour response was based on the World Health Organization criteria of physical examination, imaging investigations and/or pathological findings. Complete response (CR) was defined as the disappearance of all measurable disease in the limb, partial response (PR) as an incomplete regression of the tumour size by >50% and no response (NR) as a less than 50% decrease or an increase in tumour size. Overall response (OR) was defined as any response >50%.

Locoregional toxicity was evaluated according to the Wieberdink criteria: (I) no reaction; (II) slight erythema or oedema; (III) considerable erythema or oedema with some blistering, slightly disturbed motility permissible; (IV) extensive epidermolysis or obvious damage to the deep tissues, causing definite functional disturbance, and threatening or manifest compartmental syndrome; and (V) reaction that may necessitate amputation.

When calculating the rate of local recurrence, patients who had had amputations due to either early ILP complications or due to ILP failure were excluded from the denominator.

Quality assessment

The level of evidence presented in each study was categorized according to the SIGN grading system, developed by the Scottish Intercollegiate Guidelines Network. The level of evidence in the SIGN grading system ranges from ++ , high quality meta-analysis, systematic reviews of RCTs or RCTs with a low risk of bias, to 4, expert opinion.

Results

Study characteristics

A total of 18 studies were included in this review (Fig. 1), reporting outcomes for 1030 patients who underwent 1072 ILP procedures. The majority of studies (72%, 13/18, Table 1) were from European centres. One randomised controlled trial, 10 prospective studies and 7 retrospective studies were included; 78% of studies scored as SIGN grade 2 or above.

Tumour demographics

Where reported, 58% of ILPs were performed for primary disease (466/800, 12 studies, supplemental table 1). The majority of cases affected the lower limb (77%, 699/907, 14 studies). The commonest types of sarcoma treated were liposarcoma, malignant fibrous histiocytoma, synovial sarcoma and leiomyosarcoma.

ILP regimes

TNF-α with melphalan was the most commonly administered chemotherapy regime (Table 2). TNF-α doses ranged from 0.5 mg to 4 mg and melphalan from 0.5 mg/kg to 1.5 mg/kg, or 13 mg/L for upper limb and 10 mg/L for lower limb adjunct. Selected patients also underwent additional radiotherapy (34%, 250/736, 9 studies) or systemic chemotherapy (13%, 71/537, 7 studies) following ILP.
Table 1
Characteristics of included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year published</th>
<th>Country</th>
<th>Design</th>
<th>Patients</th>
<th>Median age (range), years</th>
<th>Median (range) months follow-up</th>
<th>SIGN grading of level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonvalot et al.</td>
<td>2005</td>
<td>France</td>
<td>RCT</td>
<td>100</td>
<td>(17–86)</td>
<td>24</td>
<td>1–</td>
</tr>
<tr>
<td>Bonvalot et al.</td>
<td>2009</td>
<td>France</td>
<td>P</td>
<td>100</td>
<td>43 (13–77)</td>
<td>27</td>
<td>2–</td>
</tr>
<tr>
<td>Cherix et al.</td>
<td>2008</td>
<td>Switzerland</td>
<td>R</td>
<td>51</td>
<td>(20–84)</td>
<td>22 (4–159)</td>
<td>2–</td>
</tr>
<tr>
<td>Derose et al.</td>
<td>2011</td>
<td>Rotterdam, Netherlands</td>
<td>R</td>
<td>208</td>
<td>57 (12–88)</td>
<td>144 (60–228)</td>
<td>2–</td>
</tr>
<tr>
<td>Di Filippo et al.</td>
<td>1992</td>
<td>Rome, Italy</td>
<td>P</td>
<td>70</td>
<td>–</td>
<td>45 (15–195)</td>
<td>2–</td>
</tr>
<tr>
<td>Di Filippo et al.</td>
<td>2004</td>
<td>Rome, Italy</td>
<td>P</td>
<td>14</td>
<td>50 (30–71)</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Eroglu et al.</td>
<td>2000</td>
<td>Turkey</td>
<td>R</td>
<td>14</td>
<td>43 (16–80)</td>
<td>47 (17–87)</td>
<td>2–</td>
</tr>
<tr>
<td>Grabellus et al.</td>
<td>2009</td>
<td>Essen, Germany</td>
<td>P</td>
<td>47</td>
<td>57.8</td>
<td>24.6 (1–67)</td>
<td>3</td>
</tr>
<tr>
<td>Gutman et al.</td>
<td>1997</td>
<td>Tel Aviv, Israel</td>
<td>P</td>
<td>35</td>
<td>48 (14–80)</td>
<td>14 (2–36)</td>
<td>2–</td>
</tr>
<tr>
<td>Hayes et al.</td>
<td>2007</td>
<td>England</td>
<td>P</td>
<td>16</td>
<td>61 (39–83)</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Hoven-Gondrie et al.</td>
<td>2011</td>
<td>Groningen, Netherlands</td>
<td>R</td>
<td>98</td>
<td>56 (14–83)</td>
<td>76 (4–203)</td>
<td>2–</td>
</tr>
<tr>
<td>Moseley</td>
<td>1992</td>
<td>Portland, USA</td>
<td>P</td>
<td>20</td>
<td>54 (16–86)</td>
<td>57</td>
<td>2–</td>
</tr>
<tr>
<td>Nachmany et al.</td>
<td>2009</td>
<td>Tel Aviv, Israel</td>
<td>R</td>
<td>43</td>
<td>(22–82)</td>
<td>45.7 (1.6–118)</td>
<td>2–</td>
</tr>
<tr>
<td>Noorda et al.</td>
<td>2003</td>
<td>Netherlands, Amsterdam</td>
<td>R</td>
<td>49</td>
<td>51 (14–85)</td>
<td>26 (0–103)</td>
<td>3</td>
</tr>
<tr>
<td>Pennacchioli et al.</td>
<td>2007</td>
<td>Milan, Italy</td>
<td>R</td>
<td>88</td>
<td>54 (18–85)</td>
<td>–</td>
<td>2–</td>
</tr>
<tr>
<td>Rossi et al.</td>
<td>1994</td>
<td>Padova, Italy</td>
<td>P</td>
<td>23</td>
<td>53 (19–73)</td>
<td>15 (1–38)</td>
<td>2–</td>
</tr>
<tr>
<td>Rossi et al.</td>
<td>2004</td>
<td>Padova, Italy</td>
<td>P</td>
<td>27</td>
<td>40 (25–71)</td>
<td>33 (12–65)</td>
<td>2–</td>
</tr>
<tr>
<td>Wray</td>
<td>2011</td>
<td>Texas, USA</td>
<td>P</td>
<td>27</td>
<td>53</td>
<td>125 (112–138)</td>
<td>2–</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial; P: prospective cohort study; R: retrospective cohort study.

* Mean.

Safety and toxicity

Safety and toxicity outcomes were reported in nine studies. A mild/moderate (Wieberdink grades 2–3) toxicity reaction was reported in 64% (314/492, 5 studies) and a severe reaction (grades 4–5) in 4% (22/603, 10 studies) of cases. Pooled mortality at 30 days was 0.3% (1/292, 5 studies). Amputation was necessary due to complications within 30 days of ILP in 1.2% of cases (7/586, nine studies).

Tumour response and local resection

Where reported, 22% of cases (216/964) achieved a complete response with a wide range of 4–37% from individual studies. Amputation was necessary due to complications within 30 days of ILP in 1.2% of cases (7/586, nine studies).

Table 2

Isolated limb perfusion protocols and toxicity.

<table>
<thead>
<tr>
<th>Study</th>
<th>Melphalan (or other anti-mitotic) dose</th>
<th>Adjunct dose of TNF-α (mg)</th>
<th>Other therapy (°C)</th>
<th>Hyperthermia</th>
<th>Complications following ILP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grades II–III</td>
<td>Grades IV–V</td>
</tr>
<tr>
<td>Bonvalot et al.20</td>
<td>Melphalan 13 mg/L (upper limb)</td>
<td>0.5 mg; 1 mg; 2 mg; 3 mg-4 mg</td>
<td>RT: 37, CT: 18</td>
<td>38–40</td>
<td>30 Day mortality</td>
</tr>
<tr>
<td>Bonvalot et al.30</td>
<td>Melphalan 10 mg/l limb volume 1 mg</td>
<td>38–40</td>
<td>RT: 50, CT: 14</td>
<td></td>
<td>21/100</td>
</tr>
<tr>
<td>Cherix et al.18</td>
<td>Melphalan 13 mg/L (upper limb)</td>
<td>Used, but dose not stated</td>
<td>Not stated</td>
<td>38–39.5</td>
<td>22/100</td>
</tr>
<tr>
<td>Deroose et al.28</td>
<td>Melphalan 13 mg/L (upper limb)</td>
<td>1–3 mg (upper limb)</td>
<td>Not stated</td>
<td>38–39.5</td>
<td>21/100</td>
</tr>
<tr>
<td>Grabelius et al.37</td>
<td>Melphalan 13 mg/L (upper limb)</td>
<td>1 mg (hand, foot, forearm)</td>
<td>RT: 39</td>
<td></td>
<td>57/57</td>
</tr>
<tr>
<td></td>
<td>11 mg (lower limb)</td>
<td>2 mg (arm, lower/dim leg)</td>
<td></td>
<td></td>
<td>21/100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg (large leg, tumour  &gt;15 cm)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gutman et al.38</td>
<td>Melphalan 0.5 mg/kg (upper limb)</td>
<td>3 mg (upper limb)</td>
<td>RT: 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 mg/kg (lower limb)</td>
<td>4 mg (lower limb)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayes et al.39</td>
<td>Melphalan 0.5 mg/kg (upper limb)</td>
<td>1 mg (upper limb)</td>
<td>38.5–39.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0 mg/kg (lower limb)</td>
<td>2 mg (lower limb)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hoven-Gondrie et al.19</td>
<td>Melphalan 13 mg/L (upper limb)</td>
<td>1 mg (axillary, popliteal)</td>
<td>38.5–40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/L (lower limb)</td>
<td>2 mg (iliac, femoral)</td>
<td>IFN-γ: 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nachmany et al.31</td>
<td>Melphalan 1 mg (upper limb)</td>
<td>26 patients, 3 mg (upper limb), 4 mg (lower limb).</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 mg (lower limb)</td>
<td></td>
<td></td>
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<tr>
<td>Noorda et al.41</td>
<td>Melphalan 10–13 mg/L</td>
<td>17 patients - 1 mg</td>
<td>IFN-γ: 5, RT: 23</td>
<td>38–40</td>
<td>1/48</td>
</tr>
<tr>
<td>Wray23</td>
<td>TNF-α, melphalan 13 mg/L (upper limb)</td>
<td>Used, but dose not stated</td>
<td>RT: 38–40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/L (lower limb)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pennacchioli et al.22</td>
<td>Melphalan, doxorubicin, IFN-γ</td>
<td>51 patients: 1 mg (upper limb), 100 mg lower limb; IFN-γ (5 patients: 0.2 mg 2 days before and during ILP), 26 patients, 3 mg (upper limb), 4 mg (lower limb).</td>
<td>38–40</td>
<td>RT: 18, CT: 13</td>
<td>4/88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rossi et al.42</td>
<td>Soxorubicin Melphalan (0.8 mg/kg), actinomycin D (n = 50), cisplatin (n = 22), doxorubicin (n = 8)</td>
<td>40</td>
<td>RT: 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Filippo et al.14</td>
<td>Soxorubicin melphalan, actinomycins D (n = 50), cisplatin (n = 22), doxorubicin (n = 8)</td>
<td>Not used</td>
<td>41.5–41.8</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Filippo et al.15</td>
<td>Doxorubicin 10–18 mg/L to establish maximum tolerated dose</td>
<td>Not used</td>
<td>41.5</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eroglu et al.36</td>
<td>Cisplatin, doxorubicin</td>
<td>Not used</td>
<td>41–42</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moseley40</td>
<td>Cisplatin 0.75–2.5 mg/kg</td>
<td>Not used</td>
<td>40–42</td>
<td>RT: 11, CT: 2</td>
<td>0.37</td>
</tr>
<tr>
<td>Rossi et al.26</td>
<td>Doxorubicin 0.7 mg/kg (upper limb)</td>
<td>Not used</td>
<td>40–42</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4 mg/kg (lower limb)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TNF-α: tumour necrosis factor-alpha; IFN-γ: interferon-gamma; RT: radiotherapy; CT: chemotherapy.

a After ILP.
b After resection of unifocal disease.
studies (15 studies, supplemental table 2). Partial response was reported in 48% of cases (434/899, range 21–64%, 14 studies), leading to an overall response rate of 72% (range 29–91%).

Local resection following ILP was possible for 72% of patients (556/774, 11 studies, Table 3). A negative resection margin (R0) was achieved in 61% (276/456) of cases and a positive margin (R1/2) in 39% (180/456).

Amputation rate

In all studies the indication for performing ILP was unresectable disease. ILP failed to induce sufficient tumour regression to allow local resection or conservative management in 11% of patients (105/960, 15 studies), who thus required amputation. After median follow-up times ranging from 11 to 125 months, 19% (203/1054, 16 studies, Table 3) of patients required subsequent amputation. This corresponds to a limb salvage rate of 81%, with a range from individual studies of 33–93%.

Recurrence

After median follow-up times ranging from 14 to 31 months, 27% of patients (213/781, 14 studies) who had ILP and were then managed by local resection or observation only experienced a local recurrence. There was a wide range of reported rates by individual studies, from 0 to 67% (Table 4). The median time to local recurrence ranged from 5 to 60 months.

After median follow-up times ranging from 12 to 22 months, 40% (265/657, 10 studies) of patients who had ILP developed detectable disease at a site distant from the affected limb, with rates in individual studies ranging from 14% to 85% (Table 4). One study with a median follow-up of 22 months reported distant recurrence rates by pathological response following ILP. In that study, 46% (6/13) of patients who had achieved CR, 50% (11/22) who had achieved PR, 49% (17/35) who had achieved OR and 64% (9/14) who had had NR later had a distant recurrence.

Survival

Survival data were not widely reported and if indicated, varying endpoints were provided (supplemental Table 3). Median overall survival ranged from 12 to 49 months (four studies) and median 5-year disease specific survival (DSS) from 47% to 56% (three studies). From three studies, median disease free survival (DFS) ranged from 36% to 74% at 5 years.

Two studies reported survival outcomes by resection margin status after local resection following ILP. Overall 5-year DFS in patients who had ILP and then local excision was greater in patients with R0 margins with those with R1/2 margins (80% versus 72%, p = 0.04). Five-year local DFS was greater in patients with R0 margins than those with R1/2 margins (90% versus 70%, p = 0.01). Five-year distant DFS was similar irrespective of resection margin status (52% for R0 and 53% for R1/2, p = 0.9). Five-year DSS was greater in patients with R0 resection than R1/2 (63% versus 49%, p = 0.004).

Comparative studies

Six comparative studies were included (one RCT, two prospective cohorts, three retrospective cohort studies;...
supplemental Table 4). Bonvalot compared 4 doses of TNF-α across 100 randomised patients. They found that there was no significant dose effect although higher doses may be more toxic. Hoven-Gondrie et al. found that lower and shorter doses of TNF-α were just as effective when analysed retrospectively. However, Nachmany et al. found high (3 × 4 mg) versus low (1 mg) doses were equally safe and improved survival, although this study was not randomised. Pennacchioli et al. found that adding TNF-α to either melphalan or doxorubicin improved local control. Wray found that TNF-α and melphalan had greater activity and less toxicity than doxorubicin alone.

Discussion

This study has shown that for locally advanced extremity sarcoma, ILP can achieve rates of limb salvage exceeding 80% where an amputation would otherwise be necessary. This was achieved by inducing tumour regression, with a complete response rate of 22% and an overall response rate of 72%. R0 resection following ILP was achieved in 61% of cases but subsequent locoregional recurrence rates were high.

Tumour response and limb salvage rate

The first key finding in this study was that ILP can induce a high tumour response rate including complete response, from a situation where the tumour was judged to necessitate amputation. The wide ranges seen reflect the heterogeneity of the included studies and procedures used and so they must be interpreted with caution. Furthermore, the selected studies included a wide range of pathological sarcoma types, the more aggressive and poorly differentiated of which may adversely affect response, although adequate comparable data to address this was lacking from the present studies. Additional variation is added by how the authors chose to report response, which may be the reason for the wide range. The problem will become more relevant in future trials using newer targeted therapies.

Loco-distant recurrence rate

The third key finding was that ILP was associated with high loco-distant recurrence rates, although this is not surprising. ILP is used for local control in patients often with large, high grade or recurrent tumours and will not treat systemic micrometastases, which were not evident at the start of treatment. Although there was suggestion that primary resection of extremity sarcoma was associated with a lower recurrence rate compared to limb-preserving surgery following ILP, and that ILP followed by recurrence incurred a worse outcome than primary resection or amputation alone, these groups were not directly comparable for definitive conclusions to be drawn. Thijssens et al. showed that following ILP and R0 resection, adjuvant radiotherapy reduced the risk of local recurrence, which conflict with findings from Deroose et al. who found that adjuvant radiotherapy was of no further benefit following good response.
to ILP.25 However, the late morbidity following radiotherapy can be considerable and its indications require further refinement.26,27

**Long-term outcome**

Long-term survival was infrequently reported with a variety of outcome measures at differing time points. There was insufficient evidence to determine whether ILP led to a survival benefit over primary amputation. However, ILP followed by an R0 resection may lead to a survival advantage.25,28 High level, multicentre evidence regarding quality of life outcome and benefit following ILP is lacking. Deroose found no functional consequences in 64% of patients undergoing ILP, with 12% of patients reporting some impairment of function and 5% requiring crutches as a result of disability.24 Thijssens et al. found that amputation and the physician’s (rather than the patient’s) decision adversely affected quality of life.29 Further long-term morbidity is introduced by early complications, early failure and late toxicity, which may be frequent.27

Along with its potential benefits, ILP also carries risks. Only 3% of patients in this review suffered a severe locoregional toxicity reaction. The amputation rate within 30 days due to ILP complications was 1.2%. This could be considered as being acceptably low given that subsequent limb salvage was over 80% in a population with otherwise unsalvageable limbs. With 64% suffering a mild/moderate toxicity reaction and 4% a severe reaction, the optimum modality of delivery of ILP (in terms of drug combinations and doses, temperature, duration and venous return) may require further optimisation.

The comparative studies were not able to determine optimum dose or combination of ILP chemotherapeutic agents. The randomised study by Bonvalot20 suggested that higher doses of TNF-α are more toxic than low doses and that there is no dose–effect relationship, a finding confirmed recently in a retrospective study by Hoven-Gondrie27 and by a further prospective phase II study in a larger patient cohort.30 The other comparative studies included in this review were based on small, retrospectively analysed cohorts with conflicting findings.19,21 Although few direct comparisons have been made, it is possible that melphalan with TNF-α is the optimum combination.5

The main limitation of this study was the lack of prospective data from high patient numbered studies. The range of different histological subtypes is common to many publications on sarcomas but ignores the fact that there is a difference in responsiveness to chemotherapy between different subtypes.

**Suggested use of ILP**

The data presented suggest that ILP should be used in a neo-adjuvant setting to allow patients, who could only otherwise be treated by radical surgery or amputation, to undergo local resection with the possibility of long-term disease free survival. It can also be used in the palliative setting, in patients with metastatic disease to achieve local control but this must be balanced against the rare but serious severe toxicity events.31,32 ILP cannot prevent the development of distant disease. The recent randomised trial of 351 patients assigned to either adjuvant chemotherapy (versus no chemotherapy) showed no benefit in relapse-free survival or overall survival.33

A range of new cytotoxic drugs is now available, in addition to a host of biological therapies, including antiangiogenics, although further evidence of their efficacy and risks is required. Other techniques such as isolated limb infusion used in the treatment of melanoma and intraarterial infusion have shown promise in sarcoma with the potential for lower toxicity rates, but they exhibit lower response rates concerning sarcoma.

**Conclusions**

This study has found that ILP is safe, induces a high tumour response rate, leads to a high limb salvage rate, but is associated with a high recurrence rate both locally and systemically. Although the majority of patients will die of their disease, ILP can provide a limb-sparing alternative to amputation when local control is necessary. Questions that still remain include the optimum dose of TNF-α and the impact of new drugs. Further work is required with any future trials being best performed by international collaboration between centres due to the rarity of the condition.

**Contributors**

A.B. took part in conceptualisation, literature review, data extraction, analysis and writing of the manuscript. L.B. took part in literature review, data extraction, analysis and writing of the manuscript. D.N. took part in literature review, data extraction, analysis and writing of the manuscript. D.G. took part in conceptualisation, analysis and writing of the manuscript. A.D. took part in conceptualisation, data extraction, analysis and writing of the manuscript. All authors were involved in the decision to submit for publication.

**Conflict of interest**

None.

**Funding**

None.

**Acknowledgements**

None.
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejso.2012.12.018.

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