Review

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

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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.

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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 colleagues[8] 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.[10] 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[11,12] and thorough reviews exist for the use of ILP in extremity sarcoma, a formally conducted systematic review focussing solely on sarcoma is lacking.[5,13] 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.[14]

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[15]: (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.[16] The level of evidence in the SIGN grading system ranges from 1++, 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.
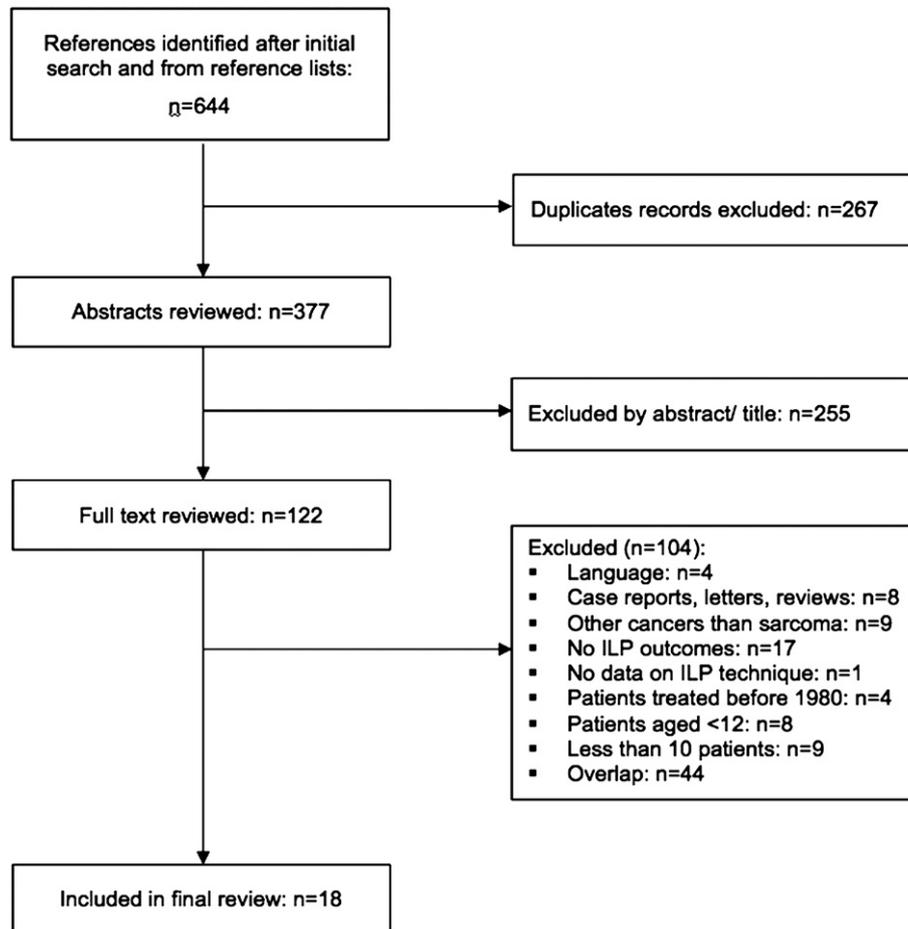
Figure 1. Flowchart of included studies.

Table 1
Characteristics of included studies.

Author	Year published	Country	Design	Patients	Median age (range), years	Median (range) months follow-up	SIGN grading of level of evidence
Bonvalot et al.[20]	2005	France	RCT	100	(17−86)	24	1−
Bonvalot et al.[30]	2009	France	P	100	43 (13−77)	27	2−
Cherix et al.[18]	2008	Switzerland	R	51	(20−84)	22 (4−159)	2−
Deroose et al.[28]	2011	Rotterdam, Netherlands	R	208	57 (12−88)	144 (60−228)	2−
Di Filippo et al.[34]	1992	Rome, Italy	P	70	−	45 (15−195)	2−
Di Filippo et al.[35]	2004	Rome, Italy	P	14	50 (30−71)	−	3
Eroglu et al.[36]	2000	Turkey	R	14	43[a] (16−80)	47[a] (17−87)	2−
Grabellus et al.[37]	2009	Essen, Germany	P	47	57.8	24.6 (1−67)	3
Gutman et al.[38]	1997	Tel Aviv, Israel	P	35	48[a] (14−80)	14 (2−36)	2−
Hayes et al.[39]	2007	England	P	16	61 (39−83)	14	3
Hoven-Gondrie et al.[19,27]	2011	Groningen, Netherlands	R	98	56 (14−83)	76 (4−203)	2−
Moseley[40]	1992	Portland, USA	P	20	54 (16−86)	57	2−
Nachmany et al.[21]	2009	Tel Aviv, Israel	R	43	(22−82)	45.7[a] (1.6−118)	2−
Noorda et al.[41]	2003	Netherlands, Amsterdam	R	49	51[a] (14−85)	26 (0−103)	3
Pennacchioli et al.[22]	2007	Milan, Italy	R	88	54 (18−85)	−	2−
Rossi et al.[26]	1994	Padova, Italy	P	23	53 (19−73)	15 (1−38)	2−
Rossi et al.[42]	2004	Padova, Italy	P	27	40 (25−71)	33 (12−65)	2−
Wray[23]	2011	Texas, USA	P	27	53[a]	125 (112−138)	2+

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

Table 2
Isolated limb perfusion protocols and toxicity.

Study	Isolated limb perfusion protocol					Complications following ILP		
	Melphalan and/or other anti-mitotics)	Melphalan (or other anti-mitotic) dose	Adjunct dose of TNF-α	Hyperthermia (°C)	Other therapy	Wieberdink toxicity		30 Day mortality
						Grades II—III	Grades IV—V	
Bonvalot et al.[20]	Melphalan	13 mg/L (upper limb) 10 mg/L (lower limb)	0.5 mg; 1 mg; 2 mg; 3—4 mg	38—40	RT: 37, CT: 18	38/100	1/100	—
Bonvalot et al.[30]	Melphalan	10 mg/l limb volume	1 mg	38—40	RT: 50, CT: 14	21/100	1/100	0
Cherix et al.[18]	Melphalan	Not stated	Used, but dose not stated	Not stated	RT: 5, CT: 11	57/57	4/57	—
Deroosee et al.[28]	Melphalan	13 mg/L (upper limb) 10 mg/L (lower limb)	1—3 mg (upper limb) 1—4 mg (lower limb)	38—39.5	RT: 72[a], 55[b]	180/208	6/208	—
Grabellus et al.[37]	Melphalan	13 mg/L (upper limb) 11 mg/L (lower limb)	1 mg (hand, foot, forearm) 2 mg (arm, lower/slim leg) 3 mg (large leg, tumour >15 cm)	39	RT: 14, CT: 13	—	—	—
Gutman et al.[38]	Melphalan	1 mg/kg (upper limb) 1.5 mg/kg (lower limb)	3 mg (upper limb) 4 mg (lower limb)	39	—	—	—	—
Hayes et al.[39]	Melphalan	0.5 mg/kg (upper limb) 1.0 mg/kg (lower limb)	1 mg (upper limb) 2 mg (lower limb)	38.5—39.5	—	—	—	—
Hoven-Gondrie et al.[19,27]	Melphalan	13 mg/L (upper limb) 10 mg/L (lower limb)	1 mg (axillary, popliteal) 2 mg (iliac, femoral)	38.5—40	IFN-γ: 20	—	—	0
Nachmany et al.[21]	Melphalan	1 mg (upper limb) 1.5 mg (lower limb)	26 patients. 3 mg (upper limb), 4 mg (lower limb). 17 patients - 1 mg	39	—	—	—	—
Noorda et al.[41]	Melphalan	10—13 mg/L	3—4 mg	38—40	IFN-γ: 5, RT: 23	—	1/48	1
Wray[23]	TNF-α, melphalan	13 mg/L (upper limb) 10 mg/L (lower limb)	Used, but dose not stated	38—40	—	—	—	—
Pennacchioli et al.[22]	Melphalan, doxorubicin, IFN-γ	melphalan (51 patients: 50 mg upper limb, 100 mg lower limb); IFN-γ (5 patients: 0.2 mg 2 days before and during ILP	1 mg	38—40 (TNF-α, n = 51); 40—41 (no TNF-α, n = 37)	RT: 18, CT: 13	—	4/88	—
Rossi et al.[42]	Soxorubicin	8.5 mg/L	1 mg	40	—	18/27	2/27	0
Di Filippo et al.[34]	melphalan, actinomycin D (n = 50), cisplatin (n = 22), doxorubicin (n = 8)	Melphalan (0.8 mg/kg), actinomycin D (0.015 mg/kg), cisplatin (2.5—5 mg/kg)	Not used	41.5—41.8	RT: 20	—	—	—
Di Filippo et al.[35]	Doxorubicin	10—18 mg/L to establish maximum tolerated dose	Not used	41.5	—	—	2/14	—
Eroglu et al.[36]	Cisplatin, doxorubicin	Cisplatin: 20 mg/l limb volume. Doxorubicin: 60 mg/m^2	Not used	41—42	—	—	0/37	0
Moseley[40]	Cisplatin	0.75—2.5 mg/kg	Not used	—	—	—	—	—
Rossi et al.[26]	Doxorubicin	0.7 mg/kg (upper limb) 1.4 mg/kg (lower limb)	Not used	40.5—42	RT: 11, CT: 2	—	1/23	—

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)[17] 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.[18] 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 than those with R1/2 margins (80% versus 72%, $p = 0.04$).[25] Five-year local DFS was greater in patients with R0 margins than those with R1/2 margins (90% versus 70%, $p = 0.01$).[19] Five-year distant DFS was similar irrespective of resection margin status (52% for R0 and 53% for R1/2, $p = 0.9$).[19] Five-year DSS was greater in patients with R0 resection than R1/2 (63% versus 49%, $p = 0.004$).[19]

Comparative studies

Six comparative studies were included (one RCT, two prospective cohorts, three retrospective cohort studies;

Table 3
Post-ILP surgical interventions.

Study	Local resections			Amputations			
	Local resections performed	R0 resection	R1 or R2 resections	Amputations due to complications ≤30 days following ILP	Amputations due to ILP failure	Total amputations at follow-up	Median (range) months follow-up
Bonvalot et al.[20]	71/100	35/71	36/71	–	13/100	21/100	24
Bonvalot et al.[30]	71/100	47/71	24/71	–	12/100	–	27
Cherix et al.[18]	35/51	10/35	25/35	–	7/51	12/51	22 (4–159)
Deroosee et al.[28]	109/208	63/109	46/109	1/210	20/210	41/210	144 (60–228)
Di Filippo et al.[34]	55/70	–	–	–	15/70	17/70	45 (15–195)
Di Filippo et al.[35]	13/14	–	–	0/14	1/14	1/14	20
Eroglu et al.[36]	12/14	–	–	0/14	2/14	2/14	*47 (17–87)
Grabellus et al.[37]	47/47	33/47	14/47	0/47	5/47	8/47	24.6 (1–67)
Gutman et al.[38]	–	–	–	–	4/35	5/35	14 (2–36)
Hayes et al.[39]	–	–	–	1/16	0/16	5/16	14
Hoven-Gondrie et al.[19,27]	92/98	72/92	20/92	1/98	7/98	24/98	11 (3–125)
Nachmany et al.[21]	–	–	–	4/43	2/43	14/43	(1.6–118)
Noorda et al.[41]	31/49	16/31	15/31	0/49	8/49	13/49	26 (0–103)
Pennacchioli et al.[22]	–	–	–	–	7/88	15/88	–
Rossi et al.[26]	–	–	–	0/23	2/23	2/23	15 (1–38)
Rossi et al.[42]	20/23	–	–	–	–	5/27	33 (12–65)
Wray[23]	–	–	–	–	–	18/27	125 (112–138)
Total	556/774	276/456	180/456	17/586	105/960	203/1054	

No data are available for Moseley.[40]

Table 4
Local and distant recurrences.

Study	Local recurrences		Distant recurrences	Follow-up (months)
	After initial local resection or conservative management	Median (range) months to recurrence		
Bonvalot et al.[20]	24/87	13	—	—
Bonvalot et al.[30]	14/87	—	25/95	27
Cherix et al.[18]	18/44	20.3[a] (2—78)	27/51	12.5 (2—43)
Deroosee et al.[28]	70/187	12 (1—170)	78/179[b]	144 (60—228)
Di Filippo et al.[35]	0/13	—	2/14	—
Grabellus et al.[37]	5/42	—	14/47	—
Gutman et al.[38]	5/31	9 (3—12)	8/35	—
Hayes et al.[39]	10/15	5 (1—17)	—	—
Hoven-Gondrie et al.[19,27]	15/90	8 (3—99)	42/98	—
Moseley[40]	1/20	60	—	—
Nachmany et al.[21]	15/36	18.8[a]	—	—
Noorda et al.[41]	—	13.5 (6—32)	—	—
Pennacchioli et al.[22]	27/81	—	38/88	—
Rossi et al.[26]	6/21	—	8/23	—
Rossi et al.[42]	3/27	33 (12—65)	—	—
Wray[23]	—	—	23/27	125 (112—138)
Total	213/781		265/657	

No data are available for Di Filippo et al.[34] and Eroglu et al.[36]
 [a] Mean.
 [b] Data are only for patients treated with curative intent.

supplemental Table 4). Bonvalot compared 4 doses of TNF-α across 100 randomised patients.[20] 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.[19] 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.[21] Pennacchioli et al.[22] 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.[23]

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.

The second key finding was the high limb salvage rate, which was afforded by the high tumour response rate. The limb salvage rate in this study is associated with an R0 resection rate of 61%, although as previously shown, this may not translate into improved survival.[6,7]

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,[24] 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 on 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 Bonvalot[20] 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-Gondrie[27] 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 anti-angiogenics, although further evidence of their efficacy and risks is required. Other techniques such as isolated limb infusion used in the treatment of melanoma and intra-arterial 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.

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.

References

1. Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. *Sarcoma* 2010;506182.

2. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978—2001: an analysis of 26,758 cases. *Int J Cancer* 2006;**119**(12):2922–30.

3. Bhangu AA, Beard JA, Grimer RJ. Should soft tissue sarcomas be treated at a specialist centre? *Sarcoma* 2004;**8**(1):1–6.

4. Creech Jr O, Krementz ET, Ryan RF, Winblad JN. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. *Ann Surg* 1958;**148**(4):616–32.

5. Eggermont AM, de Wilt JH, ten Hagen TL. Current uses of isolated limb perfusion in the clinic and a model system for new strategies. *Lancet Oncol* 2003;**4**(7):429–37.

6. Stotter AT, A'Hern RP, Fisher C, Mott AF, Fallowfield ME, Westbury G. The influence of local recurrence of extremity soft tissue sarcoma on metastasis and survival. *Cancer* 1990;**65**(5):1119–29.

7. Gustafson P, Rooser B, Rydholm A. Is local recurrence of minor importance for metastases in soft tissue sarcoma? *Cancer* 1991;**67**(8):2083–6.

8. Lienard D, Ewalenko P, Delmotte JJ, Renard N, Lejeune FJ. High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma. *J Clin Oncol* 1992;**10**(1):52–60.

9. Eggermont AM, Schraffordt Koops H, Klausner JM, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. *Ann Surg* 1996;**224**(6):756–64.

10. Eggermont AM. Isolated limb perfusion in the management of locally advanced extremity soft tissue sarcoma. *Surg Oncol Clin N Am* 2003;**12**(2):469–83.

11. Lens MB, Dawes M. Isolated limb perfusion with melphalan in the treatment of malignant melanoma of the extremities: a systematic review of randomised controlled trials. *Lancet Oncol* 2003;**4**(6):359–64.

12. Moreno-Ramirez D, de la Cruz-Merino L, Ferrandiz L, Villegas-Portero R, Nieto-Garcia A. Isolated limb perfusion for malignant melanoma: systematic review on effectiveness and safety. *Oncologist* 2010;**15**(4):416–27.

13. Eggermont AM, Brunstein F, Grunhagen D, ten Hagen TL. Regional treatment of metastasis: role of regional perfusion. State of the art isolated limb perfusion for limb salvage. *Ann Oncol* 2004;**15**(Suppl. 4):iv107–12.

14. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**(3):205–16.

15. Wieberdink J, Benckhuysen C, Braat RP, van Slooten EA, Olthuis GA. Dosimetry in isolation perfusion of the limbs by assessment of perfused tissue volume and grading of toxic tissue reactions. *Eur J Cancer Clin Oncol* 1982;**18**(10):905–10.

16. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *Brit Med J* 2001;**323**(7308):334–6.

17. Stoeckle E, Gardet H, Coindre JM, et al. Prospective evaluation of quality of surgery in soft tissue sarcoma. *Eur J Surg Oncol* 2006;**32**(10):1242–8.

18. Cherix S, Speiser M, Matter M, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for non-resectable soft tissue sarcomas: long-term results on efficacy and limb salvage in a selected group of patients. *J Surg Oncol* 2008;**98**(3):148–55.

19. Hoven-Gondrie ML, Bastiaannet E, van Ginkel RJ, Suurmeijer AJ, Hoekstra HJ. TNF dose reduction and shortening of duration of isolated limb perfusion for locally advanced soft tissue sarcoma of the extremities is safe and effective in terms of long-term patient outcome. *J Surg Oncol* 2011;**103**(7):648–55.

20. Bonvalot S, Laplanche A, Lejeune F, et al. Limb salvage with isolated perfusion for soft tissue sarcoma: could less TNF-alpha be better? *Ann Oncol* 2005;**16**(7):1061–8.

21. Nachmany I, Subhi A, Meller I, et al. Efficacy of high vs low dose TNF-isolated limb perfusion for locally advanced soft tissue sarcoma. *Eur J Surg Oncol* 2009;**35**(2):209–14.

22. Pennacchioli E, Deraco M, Mariani L, et al. Advanced extremity soft tissue sarcoma: prognostic effect of isolated limb perfusion in a series of 88 patients treated at a single institution. *Ann Surg Oncol* 2007;**14**(2):553–9.

23. Wray CJ, Benjamin RS, Hunt KK, Cormier JN, Ross MI, Feig BW. Isolated limb perfusion for unresectable extremity sarcoma: results of 2 single-institution phase 2 trials. *Cancer* 2011;**117**(14):3235–41.

24. Thijssens KM, van Ginkel RJ, Pras E, Suurmeijer AJ, Hoekstra HJ. Isolated limb perfusion with tumor necrosis factor alpha and melphalan for locally advanced soft tissue sarcoma: the value of adjuvant radiotherapy. *Ann Surg Oncol* 2006;**13**(4):518–24.

25. Deroose JP, Burger JW, van Geel AN, et al. Radiotherapy for soft tissue sarcomas after isolated limb perfusion and surgical resection: essential for local control in all patients? *Ann Surg Oncol* 2011;**18**(2):321–7.

26. Rossi CR, Vecchiato A, Foletto M, Nitti D, Ninfo V, Fornasiero A, et al. Phase II study on neoadjuvant hyperthermic-antiblastic perfusion with doxorubicin in patients with intermediate or high grade limb sarcomas. *Cancer* 1994;**73**(8):2140–6.

27. Hoven-Gondrie ML, Thijssens KM, Geertzen JH, Pras E, van Ginkel RJ, Hoekstra HJ. Isolated limb perfusion and external beam radiotherapy for soft tissue sarcomas of the extremity: long-term effects on normal tissue according to the LENT-SOMA scoring system. *Ann Surg Oncol* 2008;**15**(5):1502–10.

28. Deroose JP, Eggermont AM, van Geel AN, Burger JW, den Bakker MA, de Wilt JH, et al. Long-term results of tumor necrosis factor alpha- and melphalan-based isolated limb perfusion in locally advanced extremity soft tissue sarcomas. *J Clin Oncol* 2011;**29**(30):4036–44.

29. Thijssens KM, Hoekstra-Weebers JE, van Ginkel RJ, Hoekstra HJ. Quality of life after hyperthermic isolated limb perfusion for locally advanced extremity soft tissue sarcoma. *Ann Surg Oncol* 2006;**13**(6):864–71.

30. Bonvalot S, Rimareix F, Causeret S, et al. Hyperthermic isolated limb perfusion in locally advanced soft tissue sarcoma and progressive desmoid-type fibromatosis with TNF 1 mg and melphalan (T1-M HILP) is safe and efficient. *Ann Surg Oncol* 2009;**16**(12):3350–7.

31. Grunhagen DJ, de Wilt JH, Graveland WJ, van Geel AN, Eggermont AM. The palliative value of tumor necrosis factor alpha-based isolated limb perfusion in patients with metastatic sarcoma and melanoma. *Cancer* 2006;**106**(1):156–62.

32. Olieman AF, van Ginkel RJ, Molenaar WM, Schraffordt Koops H, Hoekstra HJ. Hyperthermic isolated limb perfusion with tumour necrosis factor-alpha and melphalan as palliative limb-saving treatment in patients with locally advanced soft-tissue sarcomas of the extremities with regional or distant metastases. Is it worthwhile? *Arch Orthop Trauma Surg* 1998;**118**(1—2):70–4.

33. Woll PJ, Reichardt P, Le Cesne A, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. *Lancet Oncol* 2012;**13**(10):1045–54.

34. Di Filippo F, Giannarelli D, Botti C, et al. Hyperthermic antiblastic perfusion for the treatment of soft tissue limb sarcoma. *Ann Oncol* 1992;**3**(Suppl. 2):S71–4.

35. Di Filippo F, Cavaliere F, Anza M, et al. Liposomal doxorubicin in the perfusional treatment of advanced soft tissue limb sarcoma. *J Chemother* 2004;**16**(Suppl 5):66–9.

36. Eroglu A, Kocaoglu H, Demirci S, Akgul H. Isolated limb perfusion with cisplatin and doxorubicin for locally advanced soft tissue sarcoma of an extremity. *Eur J Surg Oncol* 2000;**26**(3):213–21.

37. Grabellus F, Kraft C, Sheu SY, et al. Evaluation of 47 soft tissue sarcoma resection specimens after isolated limb perfusion with TNF-alpha and melphalan: histologically characterized improved margins correlate with absence of recurrences. *Ann Surg Oncol* 2009;**16**(3): 676–86.

38. Gutman M, Inbar M, Lev-Shlush D, et al. High dose tumor necrosis factor-alpha and melphalan administered via isolated limb perfusion for advanced limb soft tissue sarcoma results in a >90% response rate and limb preservation. *Cancer* 1997;**79**(6):1129–37.

39. Hayes AJ, Neuhaus SJ, Clark MA, Thomas JM. Isolated limb perfusion with melphalan and tumor necrosis factor alpha for advanced melanoma and soft-tissue sarcoma. *Ann Surg Oncol* 2007;**14**(1): 230–8.

40. Moseley HS. An evaluation of two methods of limb salvage in extremity soft-tissue sarcomas. *Arch Surg* 1992;**127**(10):1169–73. discussion 73–4.

41. Noorda EM, Vrouenraets BC, Nieweg OE, van Coevorden F, van Slooten GW, Kroon BB. Isolated limb perfusion with tumor necrosis factor-alpha and melphalan for patients with unresectable soft tissue sarcoma of the extremities. *Cancer* 2003;**98**(7):1483–90.

42. Rossi CR, Foletto M, Mocellin S, et al. Hyperthermic isolated perfusion with low-dose TNFalpha and doxorubicin in patients with locally advanced soft tissue limb sarcomas. *J Chemother* 2004;**16**(Suppl. 5): 58–61.