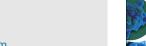


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Original Research

Isolated limb perfusion for locally advanced angiosarcoma in extremities: A multi-centre study



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KEYWORDS

Locally advanced angiosarcoma; Angiosarcoma; Isolated limb perfusion; ILP; Sarcoma; Limb salvage technique; Cutaneous angiosarcoma of the extremity **Abstract** *Background:* Angiosarcomas are rare and aggressive soft-tissue sarcomas. The only potential curative treatment is complete surgical excision. This study reports the outcome of isolated limb perfusion (ILP) with high-dose melphalan and tumour necrosis factor α for locally advanced angiosarcoma.

Material and methods: All patients who underwent an ILP for angiosarcomas between 1991 and 2016 in three tertiary referral centres were identified from prospectively maintained databases.

Results: A total of 39 patients were included, with a median follow-up of 18 months (interquartile range 6.1–60.8). Of these patients, 23 (58.9%) patients had a complete response (CR) after ILP, 10 (25.6%) had a partial response, 4 (10.3%) had stable disease and 2 (5.1%) patients had progressive disease immediately after ILP. A total of 22 patients developed local progression (56.4%), whereas nine (23.1%) developed distant metastases. The patients with CR had a significantly prolonged median local progression-free survival (PFS) (15.4 versus 7.3 months, p = 0.015) when compared with non-CR patients, and a trend towards better median overall survival (81.2 versus 14.5 months, p = 0.054). Six patients underwent multiple ILPs, whereby the CR rate of the first, second and third ILPs were 60%, 80% and 67%, respectively. Thirteen (33.3%) patients needed further surgical intervention, consisting of resection in eight patients (20.5%) and amputation in five patients (12.8%).

* Corresponding author: Sarcoma Unit, Department of Surgery, Royal Marsden Hospital, 203 Fulham Rd, Chelsea, London SW3 6JJ, UK. E-mail address: w.v.houdt@nki.nl (W.J. van Houdt). *Conclusion:* ILP is an effective treatment option for patients with locally advanced angiosarcoma in the extremities, resulting in a high number of CRs, a high limb salvage rate and prolonged local PFS.

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1. Introduction

Angiosarcomas are rare and aggressive sarcomas that account for less than 2% of all soft-tissue sarcomas (STSs) [1-3] and can occur in the subcutaneous tissue anywhere in the body. Angiosarcomas can be sporadic or can develop after previous radiation for other indications or in chronic lymphoedema in extremities (Stewart–Treves syndrome) [1,2,4]. They mostly present as a multifocal-spreading bruise with ill-defined borders [2,3]. The only curative treatment is complete surgical excision [5]. Negative surgical margins can be difficult to achieve because of the extensiveness of these sarcomas and the ill-defined borders [3]. Even with negative margins the recurrence rate is still high (26-54%) [6,7]. Consequently, many patients undergo major surgical resections requiring reconstructions and even amputations. The majority of the patients develop distant metastases at some point, with the overall 5-year survival ranging between 10% and 34% [2,3].

Isolated limb perfusion (ILP) with high-dose melphalan and tumour necrosis factor α (TNF- α) has proven to be an effective treatment for in transit melanoma and locally advanced extremity sarcoma, when function preserving radical surgery is no longer feasible [7–16]. The aim of this study was to evaluate the effectiveness of ILP as an alternative treatment option for locally advanced angiosarcoma in the extremities.

2. Material and methods

2.1. Patients

All patients undergoing ILP for angiosarcomas between 1991 and 2016 were identified from three prospectively maintained databases. The three tertiary centres included in this study were the Royal Marsden Hospital, London, United Kingdom; the Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands and Erasmus MC – Cancer Institute, Rotterdam, the Netherlands. Patient characteristics and clinical data were obtained from either the database or patient files. The size of the tumour was reported as the size of the biggest lesion on the available scans or clinical exam. Patients were stratified into those with localised disease and those with metastatic disease at presentation. All patients had extensive disease, where the only surgical option would be an (functional) amputation.

2.2. Isolated limb perfusion

The perfusion technique used has been described extensively in various articles [7-15,17,18]. Briefly, all patients were heparinised, and the targeted vessels were isolated from the systemic circulation. A tourniquet compressed collateral vessels and prevented leakage. To monitor leakage from the closed circulation, technetium-labelled albumin was added to the isolated circulation and monitored during the complete procedure. The approach for ILP could either be inguinal, femoral, axillary or brachial depending on the location of the tumour. A combination of TNF- α with melphalan was administered. After the perfusion, the limb was washed out.

2.3. Treatment, response and follow-up

Local toxicity was assessed according to the Wieberdink classification [19]. Response rates were divided into four categories according to the World Health Organisation criteria [20]. Time to local progression, systemic disease and overall survival (OS) were defined as time from ILP to the event, either noted by the patient or during follow-up. The last clinic visit or telephone call was noted as last follow-up date.

2.4. Statistical analysis

In this retrospective review, end-points were set at local progression, distant metastasis and OS. Survival data were all obtained using the Kaplan—Meier method. Differences between groups were assessed by the logrank test. A p-value of 0.05 was considered significant. Possible confounders were identified by using univariate analysis. Only confounders with a p-value below 0.1 were subsequently included in a multivariate Cox regression. Confounding factors explored were as follows: age, gender, hospital of treatment, site and type of angiosarcoma (sporadic, Stewart—Treves, radiation associated). IBM SPSS statistics, version 24 was used for the statistical analyses.

3. Results

3.1. Patients and treatment characteristics

Demographics and tumour characteristics are shown in Table 1. A total of 39 patients were included, with a

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