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Limb Salvage in Patients with Unresectable Recurrent Melanoma and Sarcoma with the Hyperthermic Isolated Limb Perfusion Technique

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Abstract

Introduction: Hyperthermic Isolated Limb Perfusion (HILP) is a surgical procedure for the regional delivery of heat and high doses of chemotherapy and biologic agents to the extremity. The procedure is employed as a limb salvage technique for locally advanced primary malignancies or recurrent cancers that are unresectable and confined to the extremity

Methods: From 1987-2016, 247 patients with unresectable recurrent melanoma (95%), sarcoma or Merkel Cell Carcinoma underwent HILP for limb salvage of the affected extremity after staging was negative for Stage IV disease and disease was confirmed to be confined to the extremity.

Results: All patients had limb salvage with this protocol. All patients were clinically negative in their regional basin at the time of perfusion, although 40% of the patients had evidence of regional nodal disease following nodal dissections. Immediate responses (within 3 months) on the extremity to the HILP were as follows: complete response (CR) of 66%, partial response (PR) of 20%, 10% stable disease and 4% progressive disease. With a mean follow-up period of 5 years, 61.5% of the patients have recurred with 68.4% of the recurrences being systemic, 21% regional nodal, 7.2% in-transit and 3.3% local-regional soft tissue.

Conclusions: HILP is an effective strategy for limb salvage in patients with unresectable, locally advanced cancers confined to the extremity. The treatment was associated with a high rate of complete responses on the extremity. Most patients recurred with distant metastases emphasizing the need for better systemic therapies for these malignancies.

Synopsis: Patients with recurrent, unresectable melanoma, other cutaneous malignancies and sarcoma confined to an extremity are problematic for clinicians since recurrence rates show that most will have occult systemic disease. An aggressive amputation approach does not make sense and the fact that these patients have active disease makes them ineligible for approved adjuvant therapies. In addition since their clinically apparent active disease is confined to the local/regional soft tissues making them Stage 3 disease, they are not eligible for Stage IV protocols. In these situations Hyperthermic Isolated Limb Perfusion (HILP) effectively treats the extremity with high response rates and a 100% limb salvage rate.

Introduction

In the treatment of malignant melanoma, recurrence due to occult metastases poses the largest threat to successful local-regional therapy [1]. With 87.5% of recurrences occurring within the local-regional distribution of the primary, this site remains the most common location for recurrence of an extremity melanoma. Isolated Limb Perfusion (ILP) was first described and performed by Creech and Krementz [2] in 1958 for the treatment of patients with locally recurrent melanoma. Considering the well-established synergistic cytotoxic effect of high heat and alkylating agent chemotherapy [3], Hyperthermic Isolated Limb Perfusion (HILP) has since become an accepted treatment for patients with in-transit or locally advanced, cutaneous extremity melanoma, featuring complete response rates of up to 70%. HILP has also been associated with high response and limb salvage rates in patients with soft tissue sarcomas [4] and has been extended to other types of skin cancer like Merkel Cell Carcinomas with recurrent, unresectable disease on an extremity.

HILP serves to maximize regional intravascular delivery of high doses of chemotherapeutic and biologic agents and synergistic heat to an extremity, while minimizing systemic effects. The most common indication for HILP is observed in the treatment of locally advanced malignancies or recurrent cancer confined to an extremity. Patients with in-transit melanoma metastases feature numerous metastatic melanoma nodules in the local-regional soft tissues of the extremity on which the primary site occurred, but have not extended beyond the regional nodal basin, based on systemic staging. These metastatic subcutaneous nodules are thought to represent intra-lymphatic spread of the melanoma and, by sheer number, make the patient unresectable. The nodules have the potential to rapidly increase in number and size, and if left untreated, may result in excessive bleeding and

ulceration. Ultimate metastases to other sites of the body outside the local/regional soft tissues would thereby render the patient Stage IV. Considering amputation of the targeted extremity rarely results in long-term survival, HILP is offered as an effective limb salvage technique.

Indeed, there are few treatment courses in medical or surgical oncology practice that yield complete response rates, for a variety of cancer types, similar in magnitude to those observed with the HILP procedure. The following report is given as the largest cohort study described in the literature documenting the proximal and longitudinal outcomes of HILP technique use in treating patients with unresectable melanoma, other skin cancers, and sarcoma confined to the extremity.

Methods

The study population consisted of 247 patients with unresectable recurrent melanoma (95%), sarcoma (4%) or Merkel Cell Carcinoma (1%) (MCC) who underwent HILP for limb salvage of the affected extremity. There were 88 women (36%) and 80% of the HILP were for lower extremity recurrences. The series was registered on a prospective database instituted at the University of South Florida from 1987-2017. The database currently has registered over 15,000 patients with a mean follow-up period of 5 years. Patients were perfused with Melphalan at a dose of 0.8 mg/kg and 1.2 mg/kg for upper and lower extremity HILP, respectively. Patients were staged with a CT scans early in the series and later with PET/CT scans to confirm that the disease was confined to the extremity.

The HILP procedure has been described previously [5,6] and is summarized only briefly here. All patients underwent a regional node dissection to gain access to the vascular supply of the extremity in order to perform the HILP and to clear the regional basin of any metastases. The dissection included a superficial groin dissection or an axillary node dissection in patients who had received a previous SLN biopsy of the respective basins. If these two procedures were previously performed, access to the extremity vessels was obtained through the iliac or subclavian vessels for leg and arm perfusions, respectively. Before infusion of Melphalan, the area of the extremity with the largest burden of disease was heated by external water jackets and the perfusion pump to a temperature of 39-41°C. Following sufficient heparinization, the main artery and vein were cannulated, and the affected limb was perfused for duration of 1 hour with Melphalan. The bypass circuit utilizes a heart-lung bypass oxygenator and cardiac bypass pump to control oxygenation, temperature, and flow of blood in the limb. Flow rates achieved during the HILP ranged from 500-1200 cc/minute.Leakage to the systemic circulation was monitored by maintaining steady volumes in the perfusion circuit. Temperature monitoring was performed in 3 areas of the extremity (foot or hand, calf or forearm, thigh or upper arm) and perfusion temperatures were maintained at 39-41 degree centigrade with cutaneous temperature probes. Toxicity was monitored by the Wieber dink grading of toxicity scale [7]. Systemic therapies that included chemotherapy and immunotherapy were employed when patients recurred systemically or when complete responses were not obtained after a post-op period of 6 months.

Regional node dissections were performed for all patients with recurrent melanoma and MCC in order to gain optimal access to the extremity vasculature supply but also to address the potential of metastatic disease in the basin.

No regional node dissections were performed in the recurrent sarcoma patients.

This study was approved by the University of South Florida Institutional Review Board.

Results

All 247 patients had limb salvage with this protocol. All patients had metastatic melanoma confined to the extremity except for 10 patients with recurrent unresectable sarcoma and 2 patients with unresectable metastatic Merkel Cell Carcinoma. Patients were clinically negative in their regional basin and all pre-op staging work-up (PET/CT scans) showed no evidence of regional nodal or systemic disease. Despite this, 40% of patients had evidence of regional disease in their nodal dissections, including those patients who were initially Sentinel Lymph Node (SLN) negative, had a complete node dissection with the HILP and were found to have occult metastatic disease in their regional basin. Immediate responses for the metastatic melanoma patients (within 3 months of the HILP) on the extremity to the HILP were as follows: Complete response (CR) of 66%, Partial Response (PR) of 20%, 10% with stable disease and 4% showing progressive disease. The 10 metastatic sarcoma patients had a CR of 50% and a PR of 30%. Both patients with metastatic Merkel Cell Carcinoma had a PR. Complications of the procedure included worsening lymphedema in 50% of patients, pain in the extremity that generally became manageable or resolved in most patients, and myoglobinuria in one patient.

Since the number of patients with sarcoma and MCC are small OS and DFS are reported for just the melanoma population. With a mean follow-up of 5 years for the melanoma patient sub-group, 61.5%

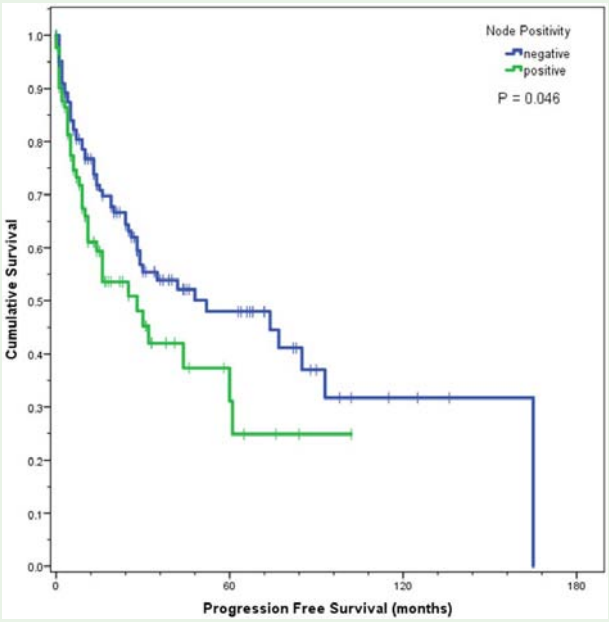

Figure 1: Disease Free Survival after a HILP in the node negative and node positive population.

Figure 2: Unresectable Recurrent Melanoma on the left foot.

Figure 4: Unresectable recurrent sarcoma - left arm.

of the patients have recurred with metastatic melanoma systemically, 21% presented with regional nodal recurrence, 7.2% have in-transit recurrences and 3.3% have presented with local-regional soft tissue recurrence.As expected disease-free and overall survival continued to be influenced by the nodal status at the time of the HILP. The 5-year Overall Survival (OS) was 28% and 58% in the node positive and node negative population, respectively ($p = 0.046$). The 5-year disease free survival was similarly influenced by nodal status being 25% in the node positive population and 47% in the node negative population ($p = 0.001$) (Figure 1). OS and DFS were calculated from the time of HILP and not from the date of original diagnosis.

Figure 2 and 3 show the course of regression of a patient with unresectable melanoma on the medial aspect of the left foot. The patient was treated with an HILP using Melphalan at a dose of 1.2 mg/kg with temperatures up to 40°C. By post-op day # 26 a CR was observed. Figure 4 & 5 show the course of a patient with a recurrent sarcoma on the left upper arm. Figure 4 is on presentation to the clinic showing the unresectable lesion, short of an amputation. By POD #45 after the HILP the patient experienced a CR and the skin defect is covered with a graft (Figure 5) [7].

Figure 5: Patient has a complete response and the wound defect is covered with a skin graft.

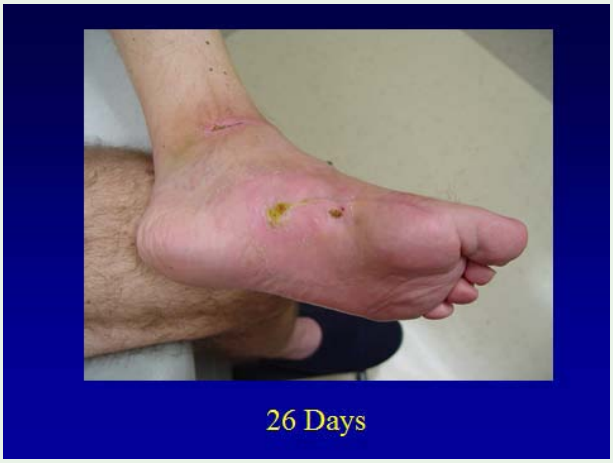

Figure 3: 26 days post HILP and the patient shows a complete response.

Discussion

The approach for patients with unresectable melanoma, other skin cancers and sarcoma confined to the extremity is a difficult one. Involving the greatest numbers in the world literature, this report details the outcomes of the HILP technique in the treatment of these patient populations and lends support to its classification as an effective limb salvage technique. Alternative treatment options for patients with unresectable metastatic melanoma are injection therapies with immunologic agents, such as BCG or Interferon. Injected lesions show rapid regression yet there is no evidence of the development of a systemic immune response to treat other lesions, particularly internal organ disease [8].

The focus of this study was on the HILP technique. The advantage of the procedure is that high doses of cytotoxic drug can be delivered to the extremity without producing systemic effects. Groups from Europe have combined cytotoxic drugs with immune active agents like TNF in attempts to increase response rates, but with added toxicity [9-11]. A similar Isolated Limb Infusion (ILI) technique is performed in

some national and international melanoma centers but the literature would suggest a lower drug delivery dose and a decreased clinical response rate with ILI [12,13]. With the HILP technique regional node dissections are necessary for the practical reason to gain access to the extremity vascular supply in order to perform the procedure. However by performing regional node dissections a clinically relevant and differentiable feature of the HILP procedure is treatment of not only the involved extremity but the regional basin, which has been shown to be clinically involved with metastatic disease in at least 40% of patients. This region is not addressed by the Isolated Limb Infusion (ILI) protocol. Indeed, HILP offers a one-time treatment option with a CR rate of 68%, which stands in sharp contrast to injection therapies requiring multiple doses and to the ILI technique defined by limited drug delivery and lower complete response rates [13]. While the HILP technique is associated with a high rate of complete responses on the extremity, as demonstrated by this report, most patients recurred with distant metastases. A need for improved systemic therapies for these malignancies is therefore indicated.

A recently approved injection therapy, known as T-Vec (Talimogene Laherpareprec), has been proposed as an alternative treatment option for unresectable Stage III or Stage IV melanoma. T-Vec is a genetically engineered, oncolytic herpes virus that has the ability to preferentially target cancer cells with no replicative ability in normal human cells [14]. Several case reports suggest a systemic immunity is produced based on tumor regression analysis [15,16]. Oncolytic virus therapy may become a first line treatment for patients with unresectable metastatic melanoma on an extremity as it is easier to administer with less toxicity. Costs may be comparable in the long term, although reported CR rates are lower than the 66-70% reported with HILP. Accompanying systemic effects would be an advantage of the T-Vec therapy. Additional longitudinal efficacy studies are needed to evidence improved patient outcomes.

In summary, there are few treatments that the medical oncologist can administer that feature CR rates of close to 70% in this setting and patient population as those provided by HILP. The less invasive infusion technique is less morbid but has a lower rate of drug delivery and lower response rates. In addition it does not effectively treat the 40% of patients that have nodal metastases at the time of in-transit metastases. Despite a new type of injection therapy approved this past year; HILP continues to have a significant and pertinent role in the treatment of these patients with recurrent and unresectable disease confined to the extremity [17].

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