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Efficacy of isolated limb perfusion (ILP) in patients with Merkel cell carcinoma (MCC): A multicenter experience

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Abstract

Background: Merkel cell carcinoma (MCC) is a rare and potentially aggressive neuroendocrine tumor of the skin, with a propensity for locoregional metastases. In two expert referral centers, isolated limb perfusion (ILP) is used to obtain locoregional control in selected locoregionally advanced MCC patients. This study describes our experience.

Method: Patients who underwent ILP for MCC were analyzed. ILP was performed with melphalan and tumor necrosis factor (TNF) combination therapy. Depending on the institution, either a normothermic or a hyperthermic temperature regimen was used. Baseline characteristics, toxicity data, locoregional progression-free survival (LPFS) and overall survival (OS) were assessed.

Results: Four males and 6 females with a median age of 78 years (IQR 61–84 years) were included. Four patients underwent ILP for upper extremity disease and 6 for lower extremity disease. All patients received combination therapy with Melphalan and TNF, one patient with the addition of interferon-gamma. No signs of systemic toxicity were present post-ILP. Severe locoregional toxicity (compartment syndrome) occurred in 1 patient and 1 elderly patient with extensive atherosclerosis had to undergo transfemoral amputation due to critical ischemia. Eight patients could be included for response evaluation. The overall response rate (ORR) was 87.5% with a complete response (CR) rate of 62.5%. Two long-term responses of 53 months and 71 months were observed. Median LPFS was 5 months and median OS was 54 months.

Conclusion: ILP shows a high CR rate that can be durable. Therefore, ILP should be considered an effective treatment modality for locally advanced MCC.

Keywords: Merkel cell carcinoma; Isolated limb perfusion; ILP; In-transit metastases; Locally advanced

Introduction

Merkel cell carcinoma (MCC) is a rare and potentially aggressive neuroendocrine tumor of the skin. It affects mostly elderly Caucasian patients, with a slight overrepresentation of males. The head and neck and extremities are predominant localizations, supporting the assumption that UV exposure increases the risk for MCC.[1,2] Other risk factors are immunosuppression and Merkel Cell Polyomavirus (MCV).[3]

MCC is a malignant disease with a high metastatic potential. At diagnosis approximately 35–40% of patients have nodal involvement.[4–6] Locoregional recurrence is seen in 26–60% of the patients, often within 2 years.[7,8] This can present as true local recurrence or in-transit metastasis (ITM); discrete cutaneous or subcutaneous intralymphatic metastases. Survival of patients with locoregionally

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recurrent disease is poor, only 39% after 3 years.[9] Therapeutic options consist of surgery and radiotherapy, chemotherapy is only indicated for patient with distant metastases.[10–13] While locoregional disease is generally managed with surgery and/or radiotherapy, there is no standard treatment for locoregionally advanced disease.[14]

In patients with locoregionally advanced melanoma, isolated limb perfusion (ILP) of the extremities proved to be safe and effective.[15,16] However, its role in patients with MCC remains unclear. Several small series showed a high complete response rate in patients with locally advanced MCC.[15,17–21] In our two melanoma and neuroendocrine expert-centers in the Netherlands, ILP is performed for patients with melanoma as well as MCC. We aimed to describe our experience with ILP in MCC patients.

Patients and methods

Patients

This study was performed in accordance with institutional ethical guidelines. All MCC patients who underwent an ILP in the Netherlands Cancer Institute (NCI) and the Erasmus MC Cancer Institute (EMC) until October 2016 were included in this retrospective cohort study.

Patient and tumor characteristics, treatment and follow-up data were obtained from patient records and collected in a database for this study.

ILP indication and technique

ILP was performed in patients with locally advanced or unresectable MCC and multiple or quickly recurring MCC in-transit metastases. The technique for ILP in melanoma has been described in detail previously.[22,23] The same technique is used for ILP in MCC. In short, the patient is placed under general anesthesia, after which the main artery and vein of the extremity are surgically accessed. The patient is heparinized and after a minimum of 2 min the artery and vein are clamped, cannulated and connected to an oxygenated extracorporeal circuit. An inflatable tourniquet ensures compression of collateral vessels to prevent systemic leakage of perfusate. Inadvertent systemic leakage is monitored by a precordial gamma probe, which detects technetium-labeled albumin added to the perfusate. Temperature probes are placed subcutaneously and in a muscle compartment. When the temperature of the extremity has reached 37 °C or 38 °C, depending on the temperature regimen used, TNF is added to the perfusion circuit. The dose of TNF used was 2–4 mg and dependent on calculated extremity volume. After 30 min, melphalan in a dose of 10 mg/L extremity volume is added to the circuit. During the procedure the temperature of the extremity is kept between 37 °C and 38 °C for normothermic ILP and between 38 and 40 °C for hyperthermic ILP. In the NCI-AvL both normothermic and hyperthermic ILP's were performed for MCC during the study period, in the EMC solely hyperthermic ILP's. One hour after the addition of melphalan, the extremity is flushed with saline and the continuity of the circulation is restored. Perfusion characteristics such as temperature, flow rate and amount of systemic leakage are recorded during the procedure.

Response rates, toxicity and complications

Response to ILP was scored according to the RECIST criteria and defined as the best overall response reached before eventual progression.[24] Local toxicity was scored according to the Wieberdink scale.[25] Complications were scored according to the Clavien/Dindo classification.[26] Patients were staged according to the AJCC 7th edition.[27]

Follow-up

Follow-up took place 6 weeks after discharge from the hospital, every 3 months for the first year, every 4 months for the second year, every six months for year 3–5 and yearly thereafter. Patients underwent physical examination during each visit. When patients presented with symptoms, they were restaged with imaging (CT or PET/CT). Relapses were scored as locoregional relapse, regional nodal relapse or distant relapse. Locoregional relapse was defined as local recurrence, satellite metastasis or an in-transit metastasis. Regional relapse was defined as regional nodal recurrence in the draining lymph nodal basin. Distant relapse was defined as subcutaneous or nodal relapse beyond the regional nodal basin or hematogenous relapse.

Statistics

The time to ILP was calculated from the date of primary MCC diagnosis to the ILP date. Survival curves were generated with the Kaplan–Meier method. MCC-specific survival (MSS) was calculated from the date of the ILP to the date of death caused by MCC or last follow-up. Locoregional progression-free survival (LPFS) was calculated from the date of the ILP to the date of the first locoregional relapse, death or last follow-up. All statistical analyses were performed using SPSS version 22.0 or STATA version 13.

Results

Patient characteristics

Ten patients (n = 10) divided evenly over our institutions, underwent ILP for MCC. Patient characteristics are shown in Table 1. Four patients were male (40%). The median age at the time of ILP was 78 years (IQR 61–84 months). Four patients underwent ILP for upper extremity disease and 6 for lower extremity disease. The median time from diagnosis of the primary tumor until the ILP