



Isolated Limb Infusion in a Pregnant Patient with Sarcoma of the Upper Extremity: A Case Report with Literature Review

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Abstract

Several scientific publications have shown Isolated Limb Infusion (ILI) as a promising treatment option for patients with soft tissue sarcomas. This minimally invasive technique has a high complete response rate (42-90%) and could serve as a neo-adjuvant treatment for limb sparing sarcoma surgical treatment to increase the likelihood of R0 resection. ILI technique has low levels of systemic leak (< 1%) and systemic toxicity rate, which makes this treatment potentially relevant in pregnant patients when radiation therapy is not an option. This is the first experience of using the ILI procedure in a pregnant woman with soft tissue sarcoma of the limb.

A 37-year-old woman was diagnosed with undifferentiated stage III (T2bN0M0G3), deep sarcoma of the left forearm. The patient was in early second trimester of pregnancy and intended to keep the pregnancy. The case was discussed at a multidisciplinary conference and the decision was to consider ILI in neoadjuvant setting to permit limb-preserving surgery since radiation therapy was rejected by patient. ILI procedure with heated melphalan (10 mg/l) and dactinomycin (100 mcg/l) was performed with good radiological response. One month later patient had a successful resection of the tumor that showed significant treatment effect from regional chemotherapy. Five months after the ILI procedure, the patient delivered a healthy 9 lb 4 oz baby.

ILI procedure is one of the available options in difficult clinical situations, such as pregnancy in a patient with deep high-grade soft tissue sarcoma of the limb to facilitate margin negative resection and provide good local control.

Keywords

Isolated limb infusion, Sarcoma, Pregnant

tissue sarcomas. At the same time, low rates of systemic toxicity [1,2,4] due to low systemic drug leakage [5] makes ILI a relevant treatment option for pregnant patients who have rejected radiotherapy and when R0 resection has been deemed problematic. The purpose of this case report is to demonstrate the first experience of an ILI procedure in a pregnant woman.

A systematic PubMed search was performed for studies reporting outcomes and systemic toxicity rates of isolated limb infusion for soft tissues sarcomas, before a treatment plan was established. Search terms used included “isolated limb infusion” separately, and in combination with “sarcoma”.

The risks of fetal injury from ILI were discussed with a maternal-fetal medicine specialist in formal consultation, with specific reference to previously documented leakage rates and the patient was extensively counseled. Ultimately, it was considered appropriate to perform the ILI procedure for this 37-year-old pregnant woman with a high-grade, deep sarcoma of the forearm.

Case Presentation

A 37-year-old left-handed Caucasian woman was diagnosed with Stage III (T2b, N0, M0, G3) undifferentiated deep sarcoma of the left forearm. A dime size mass was noticed, as long as two years before diagnosis, which rapidly enlarged during pregnancy to a 14 x 4.5 x 4.3 cm tumor. The biopsy revealed a high-grade pleomorphic undifferentiated sarcoma. The patient reported mild pain of the forearm without any decrease in passive or active range of motion. The metastatic work-up was negative. At the time of presentation, the patient was in the second trimester (14th week) of pregnancy. The patient was adamant that she did not want to terminate the pregnancy. In addition to discussing the case at a multidisciplinary sarcoma conference, the patient's obstetrician and a maternal fetal medicine specialist were consulted. After evaluation of preoperative imaging by the operating surgeon, a “low” likelihood of R0 resection was estimated due to a complex mass occupying almost the entirety of carpi ulnaris. Neoadjuvant radiation, which would normally be recommended to preserve the limb and its function and increase the possibility of negative resection margins, was not an option due to the patient's concern about unavoidable internal scatter [6] and

Introduction

Achieving recurrence free local control is one of the major goals of soft tissue sarcoma (STS) treatment. Loco-regional chemotherapy procedures, such as Isolated Limb Infusion (ILI) and Isolated Limb Perfusion (ILP), have shown high response rates of 42% to 90% [1-3] and limb preservation rates up to 98% [1] in patients with STS. However, neither ILI nor ILP has been reported in pregnant patients with soft

Citation: Milovanov V, Wodago FM, Sittig M, Gushchin V (2016) Isolated Limb Infusion in a Pregnant Patient with Sarcoma of the Upper Extremity: A Case Report with Literature Review. Clin Med Rev Case Rep 3:149

Received: October 31, 2016; **Accepted:** December 15, 2016; **Published:** December 19, 2016

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potential for fetal injury. The patient proceeded with preoperative ILI as the neo-adjuvant approach.

The standard ILI protocol was modified to exclude the use of X-rays. Five French catheters in the brachial vein and artery were placed under ultrasound guidance. Melphalan and dactinomycin doses were calculated at 10 mg/L and 100 mcg/L respectively, for the estimated volume of the limb, distal to the cuff. The patient was systemically anticoagulated with heparin and the cuff was inflated. The infusion was performed for 30 minutes with skin temperatures between 37.7 °C-38.5 °C and muscle temperatures between 37.1 °C-38.1 °C.

After completion of the ILI, 1,200 mL of lactated Ringer's was used to wash out the blood and chemotherapy agents, and the tourniquet was taken down. Total ischemic time was 50 minutes. Anticoagulation was reversed with protamine sulfate and the catheters were removed.

In the immediate postoperative period, the patient developed a hematoma at the catheter site and asymptomatic brachial artery thrombosis, which was managed with systemic anticoagulation. No embolectomy or vascular reconstruction was recommended, as she had competent collaterals. Adrenocorticoid steroids were started due to a rise in CPK above 1000 mcg/L. No grade IV/V Wieberdink toxicity [7] occurred (Table 1).

One month after the ILI procedure, the patient underwent a radical resection of the tumor with exploration and neuroplasty of the left ulnar nerve and exploration of left ulnar artery. She was found to have a dense neurapraxia of the ulnar nerve and a less pronounced neurapraxia of the median nerve, which was thought to be due to the hematoma. Three months postoperatively, the patient had significant recovery of the median nerve but ulnar nerve function had not returned. The patient did not demonstrate any clinical signs of compartment syndrome and the pattern of nerve dysfunction was clearly anatomically related to an injury in the distal medial nerve.

Histological examination of the resected specimen revealed extensive necrosis, estimated at 85%, with all relevant deep margins negative. Five months after the ILI procedure, the patient delivered a healthy 9 lb 4 oz baby at 39 weeks gestation. The baby has followed normal developmental milestones and remained healthy at 31 months follow-up and the patient remained with no evidence of disease 36 months after the procedure. The "claw hand" from the ulnar nerve palsy persisted despite return of the nerve function: the flexor muscles fibrosed with shortening of the tendons. A tendon lengthening procedure is planned to improve the extension of the tendons.

Table 1: Wieberdink grading of limb toxicity [7].

Grade I	No subjective or objective evidence of reaction
Grade II	Slight erythema and/or edema
Grade III	Considerable erythema and/or edema with some blistering; Slightly disturbed motility
Grade IV	Extensive epidermolysis and/or obvious damage to the deep tissue causing definite functional disturbances; threatening or manifest compartment syndrome
Grade V	Severe reaction which may necessitate amputation

Table 2: Review of response outcomes with ILI.

Author	Year	n	Complete response rate (n)	Partial response rate (n)	Minimal response rate (n)	Overall response rate (n)	Limb salvage rate (n)	Grade IV/V toxicity	Chemo agent(s) (n)
Hegazy MA, et al. [1]*	2007	40	n/a	30% (12)	55% (22)	85% (34)	98% (39)	0%	DOX (40) L-PAM (16) MMC/L-PAM (3) L-PAM/DACT (1)
Moncrieff MD, et al. [2]	2008	21	57% (12)	33% (7)	n/a	90% (19)	76% (16)	14% (3)	MMC/DOX/CDDP (1)
Turaga KK, et al. [21]	2011	12	17% (2)	58% (7)	n/a	75% (9)	78% (11)	0%	DACT/L-PAM (12)
Vohra NN, et al. [3]	2013	17	24% (4)	18% (3)	n/a	42% (7)	71% (12)	0%	DACT/L-PAM (17)
Wong J, et al. [22]	2013	20	15% (3)	45% (9)	n/a	60% (12)	n/a	0%	DACT/L-PAM (21)

*ILI used in combination with external beam radiotherapy.

DOX: Doxorubicin; MMC: Mitomycin-C; L-PAM: Melphalan; DACT: Dactinomycin; CDDP: Cisplatin; n/a: not applicable.

Discussion

Achieving local control is a paramount goal in treating soft tissue sarcomas of the extremity [8,9]. The treatment plan typically balances the objective of preserving function, while achieving negative resection margins. The most common proven strategy in the United States is neoadjuvant radiation followed by surgery. Neoadjuvant radiotherapy combined with a surgical approach has an approximate 90% local control rate at 5-years [10-12] and good limb preservation rates (up to 97%) [13]. However, pregnant patients often avoid radiotherapy due to unavoidable internal scatter and the resulting teratogenic effects for the fetus [1].

Regional chemotherapy is another neoadjuvant treatment strategy for sarcomas of the extremities. In Europe, isolated limb perfusion with melphalan and tumor necrosis factor-alpha (TNF-α) is used successfully with an overall response rate > 72%, and 61% for R0 resection following the procedure [14]. However, a disadvantage of ILP is the potential for significant systemic leak of the alkylating agent (>10% of the drug in 12% of cases) [15]. Additionally, TNF-α is not available in the United States.

Compared to isolated limb perfusion (ILP), isolated limb infusion (ILI) is a less invasive procedure with lower rate of systemic toxicity [1,16]. Hegazy, et al. reported no systemic toxicity in ILI procedures in patients with STS [1] and the study of Brady, et al. reported only mild nausea as a symptom of systemic toxicity (51% of patients) [17]. The low systemic toxicity of the ILI procedure could be due to the negligible systemic leakage. Median systemic leak for ILI ranges from 1-2% to 7.5% [4,18], compared to 0-21% of systemic leakage during ILP [19,20]. In our particular case, systemic toxicity and potential teratogenic effects on the fetus were the major deciding factors, making ILI the preferable technique in this case. The decision to proceed with ILI was discussed with the inventor of ILI, Dr. John Thompson. He confirmed that due to low systemic leakage (< 1% in the studies of Thompson, et al.) [5,16], ILI could be safe for the fetus in pregnant patients.

Decision making in this case was challenging, however, adherence to important principles was key. All major steps were thoroughly discussed and planned prior to the first treatment. The discussion was truly multi-disciplinary including the patients obstetrician. Each specialist was able to provide the patient with a coherent point of view for the best course of action. Even then, the patient's somewhat irrational but understandable fear of consequences of radiation made the multi-disciplinary team turn to an experimental approach for primary treatment of sarcoma modality, ILI. Reasonable precautions were taken in the case of treating a rare disease in a pregnant patient by an experimental treatment to ensure the best oncological and functional outcomes and safety of the fetus by detailed discussions of the treatment plan with the opinion leaders in the field of ILI. Clear communication based on the best available evidence made the planning and execution of the treatment possible.

To evaluate the potential efficacy of the ILI procedure in STS patients, we performed a PubMed literature search, which yielded five studies with 107 patients reporting outcomes of ILI in soft tissue

sarcomas (Table 2). The overall response rate varied from 42-90%, [7,8] and the limb salvage rate ranged from 71-98% [14]. Only one patient [2] developed a Wieberdink grade IV toxicity [7]. There were no reports of amputations resulting from acute toxicity of the ILI procedure and there were no reports of severe systemic toxicity. Based on the results of the literature search, we considered the ILI procedure an effective and a relatively safe option for pregnant patients.

Conclusion

The ILI procedure is one of the relevant treatment options for pregnant patients with soft tissue sarcomas of the extremities. ILI could be considered as an effective neoadjuvant strategy in difficult clinical scenarios when radiation therapy is not an option in achieving local control.

Acknowledgements

We would like to thank Dr. John Thompson for his consultation guiding our decision to safely perform isolated limb infusion on a pregnant woman.

Declaration of Interest Statement

The authors report no conflicts of interest.

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