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NEW THERAPEUTIC OPTIONS IN THE TREATMENT OF METASTATIC LIMB SARCOMAS: A CASE SERIES

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SUMMARY

Palliative procedures are those usually used in the treatment of metastatic limb sarcoma. However given the impressive results obtained with hyperthermic isolated limb perfusion (ILP), we tested the feasibility of isolated lung perfusion (ILuP), using the same regimen. Three patients with multiple metastases from limb sarcoma were included in this study. ILP was applied in one patient resulting in limb preservation. Patients underwent 90-minute ILuP, and subsequent metastasectomy.

In all cases the procedure was completed without complications. No systemic toxicity developed. The only postoperative complication was one case of reversible interstitial and alveolar lung edema. The three patients are still alive and two of them were disease-free at a mean follow-up of 19 months.

ILuP, with TNF and Melphaln, proved to be feasible and safe.

This technique, in association with ILP, might improve long-term survival and quality of life in patients with multiple metastases from limb sarcoma.

Introduction

Sarcomas of the extremities are a heterogeneous group of tumors, for which there is no recognized “standard of care” [1].

Although they may occur at any age, they are relatively more common in children and young adults. Primary bone tumors are less common than soft tissue sarcomas (STS); the incidence being approximately one fifth that of STS [2].

Half of patients with intermediate or high-grade sarcomas develops metastatic disease [3]. The most common site of metastases from extremity sarcomas is the lung. In the presence of metastatic disease, radiotherapy or chemotherapy are usually considered the standard of care for limb sarcomas, while surgical resection of the primary tumor is considered appropriate as a palliative procedure [2].

New therapeutic options, potentially able to improve the prognosis of patients with metastatic limb sarcomas could change the global therapeutic approach to this disease and make it possible to tailor treatment according to the individual patient. Given the impressive results obtained with isolated limb perfusion (ILP) with TNF and Melphaln in patients with sarcomas of the extremities, we translated the same regimen to the treatment of lung metastases from sarcomas [4,5].

The primary aim of this preliminary study was to assess the feasibility of hyperthermic isolated lung perfusion (ILuP), with TNF and Melphalan in patients with multiple lung metastases from limb sarcomas. The secondary aim was the evaluation of both systemic and local (pulmonary) toxicity.

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Material and methods

Inclusion criteria were: (1) histologically confirmed limb sarcoma (2) multiple lung metastases; (3) performance status from 0 to 1; (4) no demonstrable extra pulmonary metastases; (5) no relapse at the primary tumor site; (6) cardiac and lung reserve consistent with the planned operation; and (7) adequate hematologic, hepatic, and renal function.

No patient was excluded on the basis of: (1) the duration of the interval between treatment of the primary tumor and appearance of neoplastic deposits in the lung or (2) the number and size of pulmonary metastases.

Preoperative evaluation included chest roentgenogram, lung and cardiovascular function evaluation, arterial blood gas measurements, computed tomography of the chest and abdomen, ultrasonography and/or magnetic resonance imaging of the primary sarcoma region, and positron emission tomography scan.

Three patients with multiple pulmonary metastases from sarcomas of the extremities were enrolled in this study: clinical and pathological data are reported in Table 1.

Two patients presented with synchronous lung metastases while the third patient developed lung metastases 32 months after treatment of the primary sarcoma.

All patients were informed about the potential benefits and hazards of this experimental treatment and gave their consent.

The primary tumor was treated as follows: one patient underwent ILP (right leg) as described in detail in the literature [4-6], followed by tumor resection with limb salvage; another patient underwent right arm compartmental resection; the third patient had a left leg amputation in an-

SEX	AGE	HYSTOLOGY	SITE	MTS (*)	FOLLOW UP (†)	PATIENT STATUS (§)
M	43	Synovial sarcoma	Right Leg	48	15	lung relapse
F	67	Mixofibrosarcoma	Right Arm	13	17	NED (‡)
M	19	Osteogenic sarcoma	Left leg	4	24	NED (‡)

(*) Number of metastasis; (†) Months since the ILuP procedure;
(§) at the last follow up; (‡) NED = no evidence of disease

Table 1: Clinical and pathological data

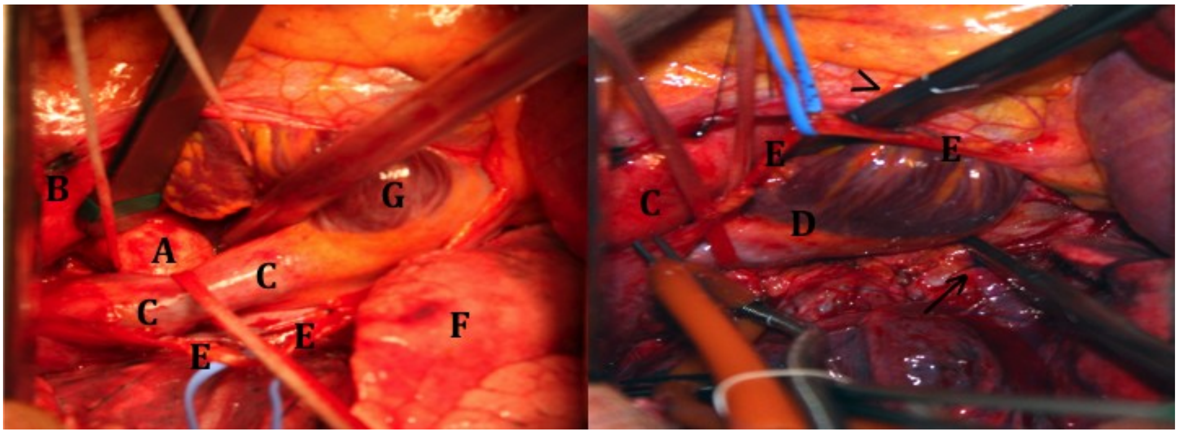

Figure 1: Intraoperative pictures of isolated right lung perfusion. The left image shows the dissection of the main right pulmonary artery (A) between the ascending aorta (B) and the superior vena cava (C) before clamping and cannulation. The right image shows a surgical clamp (>) occluding the pulmonary artery, while a second clamp (→) is placed across the left atrium (D); this second clamp creates the “atrial chamber” for cannulation. Other anatomical structures: phrenic nerve (E), right lung (F) and right atrium (G).

other hospital, where ILP was not attempted.

Two patients had bilateral lung metastases and underwent staged thoracotomies, with bilateral lung perfusion and metastasis resection, at a 4-6 week interval. At the time of the operation, regional chemotherapy was given as the first treatment modality because blood supply was still not compromised by metastasectomy.

A muscle-sparing anterolateral thoracotomy at the fifth intercostal space was used. The pulmonary artery and veins were exposed by incision of the pericardium. The left pulmonary artery was dissected free and occluded by a vascular clamp lateral to its origin. The right pulmonary artery was clamped between the ascending aorta and the superior vena cava (Figure 1). The lateral portion of the atrium was freed to allow use of a Satinsky clamp to occlude the atrial chamber draining the veins of the perfused lung. Thus the circulation of the lung to be perfused was completely isolated from the systemic circulation.

The bronchial arteries were temporarily occluded in order to prevent bronchial blood from flowing into the venous return. Polypropylene purse-string sutures were placed in the pulmonary artery and the superior pulmonary vein. Care was taken to locate the tip of the venous catheter in the atrial chamber and to avoid venous congestion. The vessels were cannulated by a 14F/16F right-angled perfusion catheter (Bard, Tewksbury, Mass.). Intravenous heparin was given (5000 units) before cannulation. The cannulas were then connected to the perfusion circuit.

The perfusion circuit consisted of a dedicated device: the Performer-HT, RanD, Medolla, Italy (Figure 2). The system is able to control different processes: extracorporeal circulation (ECC), blood oxygenation and heating. A cardiotomy reservoir and a filtration system are also included in the disposable kit. The pre-heated auxiliary fluid circulates to the heat exchanger by means of a peristaltic pump, while a second pump delivers the warmed/oxigenated blood to the lung. Venous blood coming from the lung is returned to the reservoir

Table 2: Values of the perfusion parameters

PARAMETERS	*VALUES*
Priming	**800 ml**
Heparin	**75 mg**
Perfusate pH	**7.3-7.4**
Perfusate pO_2	**170 – 185 mmHg**
Flow	**400-500 ml/min**
Pressure	**< 25 mmHg**
Inflow temperature	**40.5 – 41.5 °C**
Outflow temperature	**40 – 40.8 °C**
Perfusion duration	**90 min**
Melphalan	**30 mg**
TNF	**1 mg**

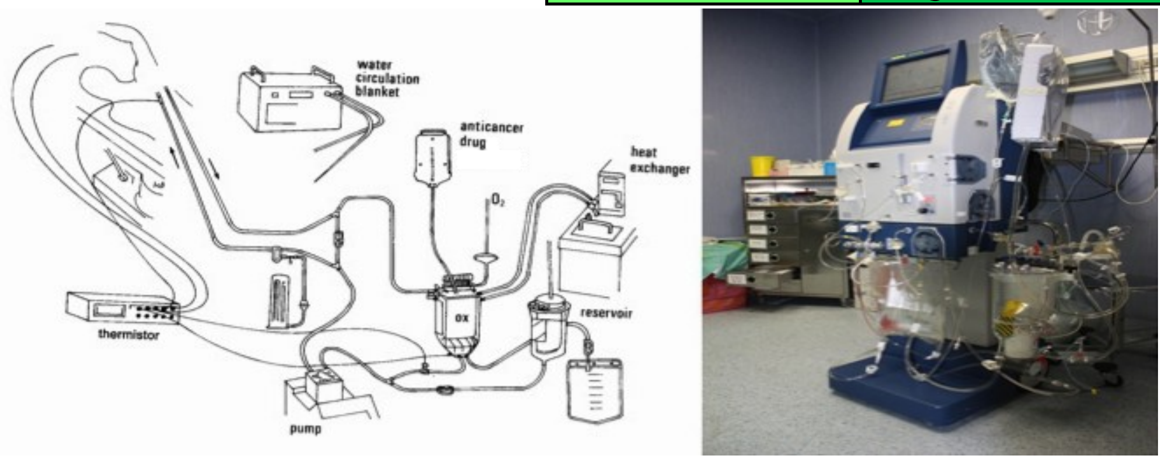

Figure 2: A schematic diagram of the perfusion circuit (data from [21]) and a photograph of the commercially available device, containing all the components of the drawing.

by gravity. A real-time monitoring system controls all the temperatures involved.
The perfusion parameters are illustrated in Table 2.
The isolated lung was ventilated during ILuP, and the perfusate was oxygenated to prevent pulmonary vasoconstriction as a result of hypoxia.
The leakage from the circuit to the systemic circulation was monitored at 5 minute intervals during the entire procedure using 99mTc-labelled erythrocytes, as illustrated in Table 3.
At the conclusion of lung perfusion, the perfusate was discarded and the circuit was washed (at the flow rate used during the perfusion) with 6000 ml of lactated Ringer's solution. The cannulas were then removed. All identified nodules were removed by means of limited resections.
Follow up was carried out at 1, 3, 6, 12 and 24 months after surgery and included clinical assessment, CT of chest and upper abdomen, and lung function evaluation (FVC: forced vital capacity; FEV1: forced expiratory volume in 1 sec.; DLCO: carbon monoxide lung diffusing capacity) and arterial blood gas values.

Results

The procedure was completed in each case, and no complications occurred during the operation.
There was no significant leakage from the

LF (leakage factor): $\frac{\text{(CPMsystemic-CPMbaseline)/CPMbaseline x Dsystemic}}{\text{Dperfusion x Vtotal/Vsystemic x 100\%}}$
CPMsystemic: systemic count observed during perfusion
CPMbaseline: systemic count rate at the beginning of the perfusion
Dsystemic and Dperfusion: doses administered in the patient's circulation and into the perfusion circuit
Vtotal: total blood volume
Vsystemic: blood volume of the patient's systemic circulation
Radiopharmaceutical: 99mTc-labelled erythrocytes
Systemic dose: generally 3 – 5 MBq
Perfusion circuit dose: 3-50 MBq

Table 3: Method for the evaluation of the of leakage during regional perfusion (modified by Stehlin et al, Arch Surg 1961;83:943-50)

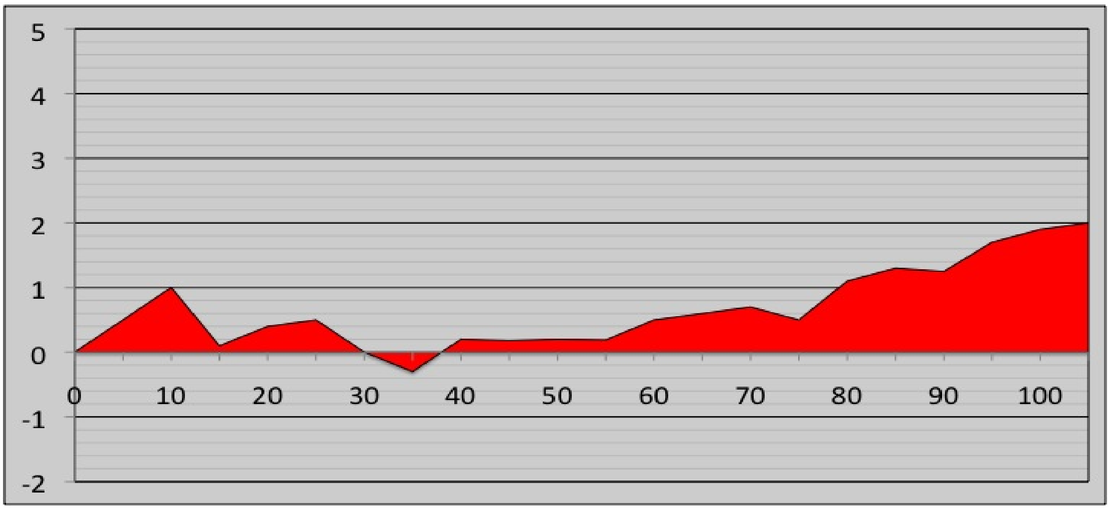

Figure 3: Leakage percentage, monitored at interval of 5 minutes over the entire procedure (t=0: starting of the procedure; t=100: end of the procedure). A value higher than the 2% has not been recorded.

circuit (less than 5%) as documented by 99mTc-labelled erythrocytes (Figure 3).
As a consequence, no systemic toxicity occurred.
The only postoperative complication (1 case) was the development, 48 hours after treatment, of radiologic signs of interstitial and alveolar edema, showing signs of the previously described "contusion syndrome" [7].
This patient recovered after 2 days of standard medical therapy. The mean hospital stay was 10 days. There was no late morbidity caused by the procedure.
Lung toxicity proved to be minimal, as shown by post operative CT (Figure 4), and transbronchial needle biopsy (Figure 5). Lung function tests showed a reduction of FVC, FEV1 and DLCO which were consistent with the reduction of lung volumes as a result of metastasectomy, as reported in Table 4.
All the patients are alive, and the follow-up times are shown in Table 1. Patient number 1 in Table 1 showed disease relapse in the lung, while the other two patients are disease-free.

Discussion
Sarcomas of the extremities may occur at any age, but they are relatively more common in children and young adults [3]. Approximately 10 % of these patients have evidence of metastatic disease after staging evaluation [8,9].
Consequently, the objective of treatment in patients with multiple lung metastases from limb sarcoma should be to improve quality of life, while offering hope of a cure.
However, presently surgery is only considered for symptom relief in these patients, while palliative radiotherapy or chemotherapy are usually considered the standard of care. Factors such as patient's symptoms (e.g., pain or fungation), co-morbidity,

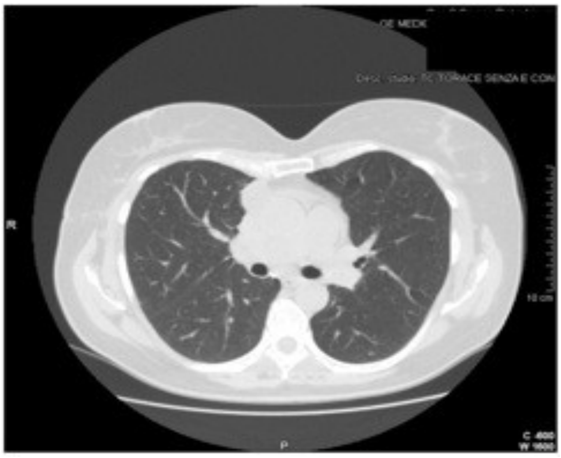

Figure 4: Postoperative CT, three months after surgery, showing a normal lung parenchyma appearance.

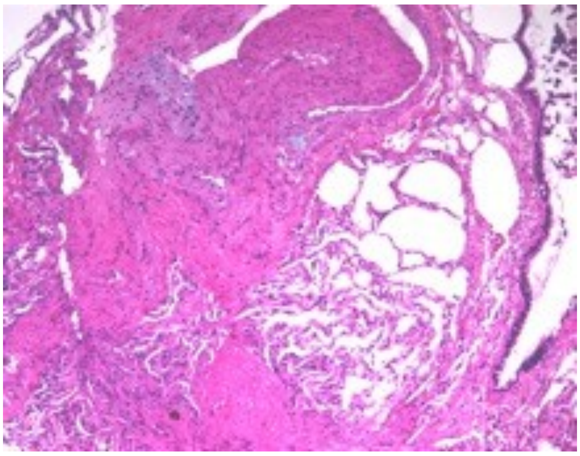

Figure 5: Transbronchial needle biopsy, 1 month after ILuP. Minimal thickening of vascular walls and mild interstitial fibrosis are shown (hematoxylin and eosin).

	FVC		FEV 1		DLCO	
	B.P.	A.P.	B.P.	A.P.	B.P.	A.P.
Patient 1	2.68 (90%)	2.43 (82%)	2.03 (82%)	1.72 (70%)	89%	61%
Patient 2	2,79 (89%)	2,63 (84%)	2,19 (84%)	1,96 (75%)	94%	79%
Patient 3	2.99 (96%)	2.83 (92%)	2.41 (91%)	2.13 (81%)	113%	85%

__FVC:__ forced vital capacity; __FEV1:__ forced expiratory volume in 1 sec; __DLCO:__ carbon monoxide lung diffusing capacity; __B.P.:__ before perfusion ; __A.P.:__ 1 month after perfusion

Table 4: Values of FVC, FEV1 and DLCO before and one month after perfusion.

histological sub type and the number of metastases are currently taken into account when planning surgery.

The palliative approach is based on the knowledge that patients with metastatic sarcoma have a poor prognosis, with a median survival of only 1.5 years [10,11].

A recent study from the Memorial Sloan-Kettering Cancer Center has shown that, despite improved insight into the tumor biology of sarcomas, the prognosis for patients with sarcomas has not improved in the last 20 years [12].

Patients with metastatic limb sarcoma often present with combined problems of locally very advanced tumors and numerous lung metastases. In these patients, new therapeutic options, such as ILP and ILuP, might offer the patient a less disabling surgery and a potential cure.

The primary tumor may be disabling and very difficult to handle because of the poor sensitivity of these tumors to systemic therapies [13]. Radiotherapy efficacy may also be limited because of the tumor size.

ILP has been demonstrated to be a valuable pre-operative technique for reducing the size of extremity tumors, where limb preservation was otherwise impossible [14].

In the present study, limb preservation by means of ILP was achieved in one out of the three patients. The third patien underwent amputation of the extremity in another Institution, where limb preservation by ILP was not attempted. In the literature, the reported ILP response rates are very high (63-91%) [7,14,15].

In keeping with the data reported by other authors, systemic toxicity from ILP in our treated patient was absent [16].

In patients with metastatic disease, any response that leads to local control and prevents amputation, without significant systemic side effects, may be particularly worthy.

This is a mandatory requirement since, in patients needing multiple staged operations, each procedure should be relatively free of complications.

ILuP, a technique allowing the delivery of high-dose chemotherapy to the lung with minimal systemic exposure, has the potential of improving prognosis and modulating the therapeutic approach in these patients.

The rationale supporting the use of ILuP in the treatment of multiple lung metastases from sarcomas rests on several concepts: 1) in the metastatic cascade; there is a phase during which the disease is limited to the lung; 2) the lung is the first district of metastatic spread in approximately 80% of sarcomas [17,18]; 3) pulmonary metastases are the primary cause of death in patients with sarcoma [19]; 4) even after a complete resection of multiple pulmonary metastases, the major recurrence site remains the lung; and 5) many patients who die with pulmonary metastatic disease have no extrathoracic spread at autopsy [18,20].

A previous study from our laboratory demonstrated the impressive pharmacokinetic advantages of ILuP with respect to the systemic administration of drugs [21].

The lung is an ideal model for isolated organ perfusion: 1) the pulmonary artery and veins can be easily clamped and cannulated, excluding the treated organ from systemic circulation; 2) the bronchial arteries drain into the pulmonary veins, preventing a systemic leak from the circuit; 3) lung metastases are largely perfused by pulmonary circulation.

ILuP associated with metastasectomy is aimed to sterilize micrometastases that are not detected during surgery.

The present study showed that hyperthermic ILuP (with TNF and Melphalan) coupled with metastasectomy is feasible, even in patients with a very high number of metastases in both lungs. No symptom or sign of systemic toxicity developed. The dreaded, shock-like symptoms of TNF leakage were absent. It is likely that the reduced systemic exposure to TNF and Melphalan, as documented by the minimal leakage from the circuit, may account for the absence of systemic toxicity. The acute lung damage was restricted to reversible pulmonary edema, which was seen in one out of the 3 patients. During the follow up period, lung function tests showed a progressive recovery of all the investigated parameters.

The concept of combining surgical excision with regional chemotherapy has been previously shown to be useful in patients with localized melanoma of the limbs [22]. The present study suggests that such a combined approach may also be applied to the lung.

Although isolated perfusion of both lungs has already been accomplished with use of

two completely separate pumping circuits [23, 24], we adopted a staged thoracotomy approach in patients with bilateral disease, in order to minimize the risk of postoperative respiratory impairment.
In the present series, the number of lung metastases was very high, ranging from 4 to 48; this finding has been consistently associated with an unfavorable outcome. In spite of this, the 3 patients are still alive and two of them are disease-free on CT scan examination, supporting the potential efficacy of the ILuP.

Conclusion

The inclusion of both ILP and ILuP in the therapeutic plan should provoke a reconsideration of the role of surgery in the treatment of limb sarcomas with multiple lung metastases. ILP could allow a radical primary tumor resection, while preserving the affected limb, and ILuP could prevent disease relapse in the lung. Such a combined approach is aimed at improving long -term survival and quality of life. Although our results are encouraging, further studies are needed to confirm feasibility and to verify the advantages of this procedure.

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