Isolated limb infusion for melanoma: a simple alternative to isolated limb perfusion

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Objective: To describe initial experience with the new technique of isolated limb infusion (ILI) for in-transit melanoma. **Design:** A prospective case series. **Setting:** The major tertiary care oncology centre for the state of Victoria, Australia. **Patients:** Nine patients having for extensive in-transit limb melanoma **Interventions:** All patients received ILI (13 treatments). **Outcome measures:** Patient survival, response to treatment and complications of treatment. **Results:** There were no perioperative deaths and morbidity was limited to deep venous thrombosis and pulmonary embolism in 1 patient. Control of the in-transit metastases was achieved to some degree in all patients and was complete in 4. **Conclusions:** ILI is an alternative treatment modality for patients suffering from multiple, advanced in-transit melanoma metastases. It provides effective palliation with limited morbidity and offers a safe, quick, inexpensive alternative to isolated limb perfusion with comparable results.

Objectif : Décrire l'expérience initiale de la nouvelle technique de perfusion sur membre isolé (PMI) dans le cas d'un mélanome en transit. **Conception :** Série de cas prospectifs. **Contexte :** Le principal centre d'oncologie tertiaire de l'État de Victoria, en Australie. **Patients :** Neuf patients atteints d'un mélanome en transit étendu à un membre. **Interventions :** Tous les patients ont reçu une PMI (13 traitements). **Mesures de résultats :** Survie du patient, réaction au traitement et complications. **Résultats :** Il n'y a eu aucun décès péri-opératoire et la morbidité a été limitée à la thrombose veineuse profonde et à l'embolie pulmonaire chez un patient. Le contrôle des métastases en transit a été réussi jusqu'à un certain point chez tous les patients et complet chez quatre patients. **Conclusions :** La PMI est un mode de traitement de substitution pour les patients atteints d'un mélanome en transit avec métastases multiples avancées. Le traitement permet une palliation efficace entraînant une morbidité limitée et offre une solution de rechange peu coûteuse, rapide et sûre à la perfusion sur un membre isolé et donne des résultats comparables.

Melanoma, a common disease worldwide, is increasing in frequency. In up to 10% of patients with advanced melanoma the curious problem of in-transit or multiple cutaneous metastases (ITM) will develop, extending from the site of the original lesion toward the regional lymph node basin. The development of in-transit metastases is related to tumour thickness and the presence of lymphatic invasion by the primary tumour. The median time to presentation with ITM is 13 to 16 months from the time of initial diagnosis. The 5-year survival has been reported as 12%, with a median survival of 19 months.[1] The quality of life for these patients is frequently poor due to multiple, ulcerating, painful lesions and a limb with considerable functional impairment. Efforts to reduce the morbidity of ITM are generally palliative.[2,3]

Surgery, radiotherapy and intralesional therapies are suitable for cases of limited ITM. Isolated limb perfusion (ILP) is usually reserved for patients with extensive, large or recurrent ITM. ILP is a complicated procedure with substantial morbidity and mortality.[2,3] Thompson and colleagues[4] from the Sydney Melanoma Unit have recently described the procedure of isolated limb infusion (ILI), which is a quicker, safer and cheaper alternative

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to ILP and offers comparable results. Briefly, the procedure involves administration of high-dose chemotherapy to a hyperthermic hypoxic limb. The chemotherapy is washed out at the conclusion of the procedure. We review the recent initial experience with ILI in Melbourne and the technical aspects of the procedure.

Patients

Patients with ITM were referred to our multidisciplinary melanoma clinic for assessment. ILI was offered to patients with multiple limb ITM. Information on all patients treated with ILI from August 1997 to April 1999, was collected in a prospective manner. This group of 9 patients had extensive disease and had previously been treated with multiple other modalities, including resection and radiotherapy. A second ILI was planned for all patients 4 to 6 weeks after the initial treatment. In patients who had a good response to the planned protocol, further treatments were considered for recurrent or persistent disease.

Surgical methods

The technique of ILI has been described by Thompson and colleagues,[4] but we summarize it here. The initial step is measurement of the volume of the limb to be infused and of the partial volumes of the affected limb that can be excluded from infusion. The major artery and vein of the limb are cannulated under fluoroscopic control in the radiology department. The distal end of the catheters are placed at the lower thigh level (or lower arm). Once the patient is suitably anesthetized, heparin, an anti-nausea serotonin antagonist and dexamethasone are administered intravenously, a heated air blanket is placed around the limb and a tourniquet is placed proximal to the tips of the catheters. Disease extending proximally to at least the mid-thigh can be effectively treated if the tourniquet is situated as high up the limb as possible. The catheters are checked for patency, connected to a 3-way stopcock and joined in a circuit. The distal limb is excluded from the infusion field with an Esmark tourniquet if the area is unaffected in order to reduce the toxicity of the procedure. Papaverine is administered to the limb via the arterial catheter. The dose of melphalan and actinomycin D is prepared proportional to the volume of the limb to be infused (melphalan 5 mg/L, actinomycin D 50 mg/L), added to 400 mL of normal saline and delivered rapidly by pressure infusion. The infusate is then circulated manually for 20 minutes in 25-mL aliquots, using a syringe and the 3-way stopcock. The limb is flushed with a litre of Hartman's solution via the arterial catheter and a similar volume is withdrawn from the venous catheter. The tourniquet is removed, followed by the catheters.[4]

Postoperatively patients remain in bed for 5 to 7 days, and creatine kinase levels are checked daily. Patients take low-dose acetylsalicylic acid daily for 3 months postoperatively.

Table 1

Details of 9 Patients With Advanced Melanoma Who Underwent Isolated Limb Infusion

Patient no.	Age, yr	Sex	Primary site	Breslow thickness, mm	Previous treatments	No. of ITM	Average size of ITM, mm
1	62	M	Foot	4	RT, chemo	40	2
2	68	M	Thigh	3	Chemo	40	2
3	67	M	Foot	0.6	Surg	200	3
4	53	M	Foot	3.4	RT ×4, chemo	10	8
5	80	F	Popliteal	19	RT ×2, surg	5	10
6	65	M	Foot	5.3	RT ×2, surg ×2, chemo	20	5
7	66	M	Foot	4.5	0	10	5
8	80	F	Ankle	7	Surg	15	8
9	83	M	Tibia	4	RT ×2, surg	8	8

RT = radiotherapy, chemo = systemic chemotherapy, surg = surgical excision ITM = in-transit metastases.

Table 2

Results of Isolated Limb Infusion (ILI) on 9 Patients Having Advanced Melanoma

Patient no.	No. of ILIs	Days F/U	Outcome	Complication	Toxicity
1	1	76	PR	None	II
2	1	113	PR	None	II
3	3	107	CR	None	II
4	1	75	PR / died	None	I
5	1	165	PR / died	None	II
6	1	534	CR	DVT, PE	III
7	2	45	PR	None	I
8	1	103	CR	None	I
9	2	540	CR	None	I

Patient 4 died of progressive systemic disease, patient 5 died of ischemic heart disease. Toxicity of limb perfusion is graded according to the Wieberdink Toxicity Scale.[5]
PR = partial response, a reduction of at least 50% in either the number or total volume of ITMs, CR = complete response, DVT = deep venous thrombosis, PE = pulmonary embolism.

Results

The results are shown in Tables 1 and 2. One patient received 3 ILIs, 2 patients received 2 ILIs, 2 patients had a second ILI planned, 2 patients had a complete response after their first ILI and 2 patients died after their first ILI. One death was attributed to progression of the disease elsewhere and the other patient died

of pre-existing cardiovascular disease. There was 1 complication of ILI, a deep vein thrombosis in the infused limb and pulmonary embolism, which occurred 6 weeks after an uncomplicated ILI. This patient remains alive and well with limited ITM 18 months after the original procedure. Toxicity was graded using Wieberdink's scale: I — no erythema or edema; II — mild, limited erythema or edema; III — considerable, marked erythema or edema, blistering; IV — extensive skin sloughing or compartment syndrome; V — severe injury necessitating amputation.[5] All patients in this series were treated for lower limb ITM. Figs. 1 to 3 illustrate the effects of a successful ILI.

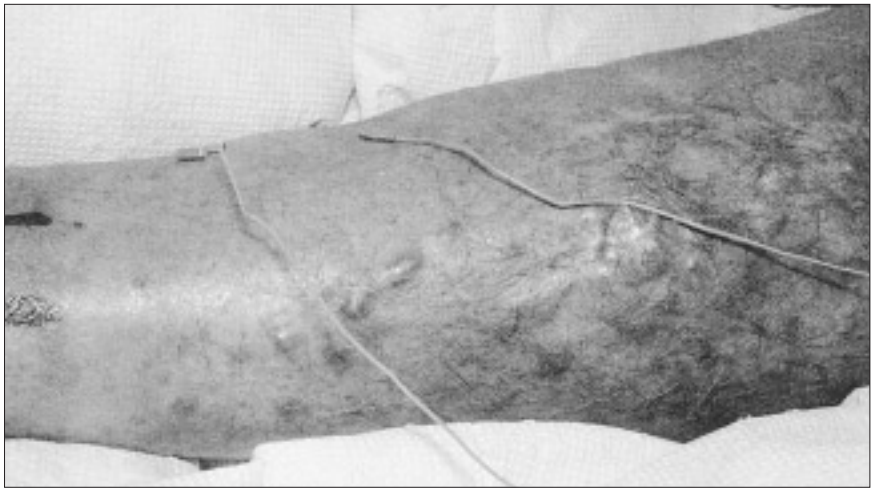

FIG. 1. The lower leg of patient no. 9 at the time of the first isolated limb infusion. In-transit metastases had developed after excision of a 4-mm thick melanoma from the left pretibial region. Despite 2 attempts at wide excision (including use of a large local flap) and radiotherapy the disease recurred and progressed. Extensive disease is present.

Discussion

ITM is commonly seen in patients with advanced melanoma. These patients often present with multiple, ulcerating, painful lesions. Depending on the severity of the disease, a number of different modalities have been used to treat ITM. Radiotherapy is appropriate for disease limited to a small area.[6] Surgical excision, intralesional therapy and cryotherapy may also be indicated if the number and size of the lesions is limited. For ITM that are recurrent, residual after other treatments or extensive, a durable alternative is needed. Traditionally, ILP, initially described in 1958 by Creech and associates,[7] has been used. In this technique, the circulation of the affected limb is isolated from the systemic circulation by means of an extracorporeal bypass pump as in cardiac surgery. High-dose chemotherapy is administered and circulated through the limb while the temperature of the limb is maintained in a hyperthermic state. Various chemotherapeutic agents have been used, but melphalan remains the most commonly used agent. ILP may be repeated electively 4 to 6 weeks after the primary treatment.[8] This is an effective modality

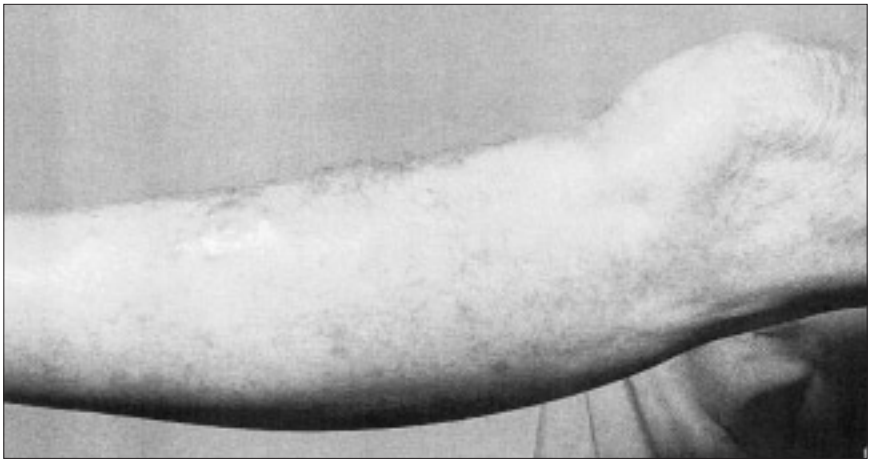

FIG. 2. Patient 9, 8 weeks later before the second Isolated limb infusion. There has been considerable regression of the in-transit metastases.

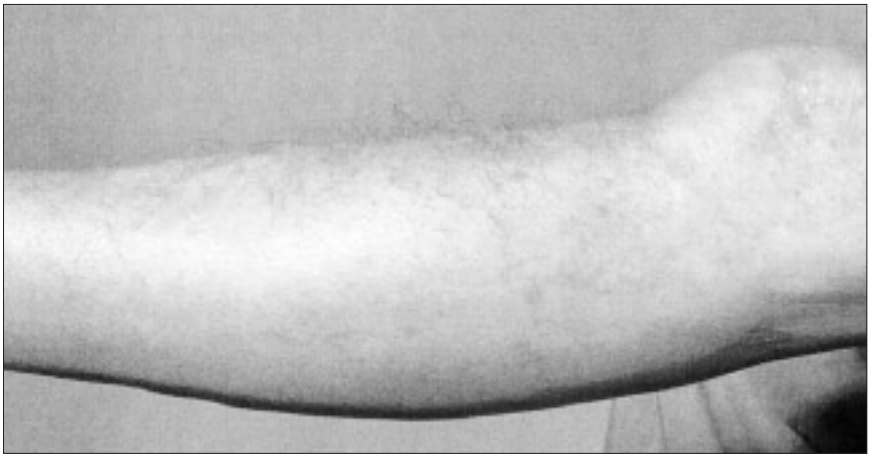

FIG. 3. Patient 9, 18 months after the second isolated limb infusion, maintains a complete response in his leg. However, by this time pulmonary metastases had developed.

for the problem of ITM, but it is expensive, labour intensive, requires specialized equipment, substantial operating room time and has the potential for significant complications. ILP results in a complete response in about 40% of patients, partial response in 40% and no response in 20% of patients treated.[2] Moderate complications, such as edema, erythema, injury to skin and adnexal structures, are common and often result in short-term disability.[2,9] Severe complications such as myopathy or neuropathy (7%), compartment syndrome, skin loss, thrombosis (5%) and even limb loss (1%) may occur. The overall morbidity of this procedure is significant.[2,10]

These early limited results are the first to duplicate the work of Thompson and colleagues,[4] who introduced the procedure of ILI. They reported a complete response rate of 45% and a partial response rate of 42%, which compares favourably with ILP. The complication rates in that study were low with no grade V reactions, and only 1 of the last 50 patients suffering a grade IV reaction.[4] In our series, we found the procedure to be effective and safe, one that can be performed by surgeons with an interest in the management of patients with melanoma. The complications are manageable and usually limited to erythema, swelling and leg pain that resolves in 10 days. The complications are not as severe as those associated with ILP. ILI can be safely performed in elderly patients or those with other serious medical problems, as was the case with 4 of our patients. Prior exposure to systemic chemotherapy in 4 patients did not appear to affect the response to ILI, nor was excessive morbidity noted in patients previously treated with radiotherapy. Two patients with known symptomatic peripheral vascular disease underwent the procedure without complication.

In-transit metastasis is a problem peculiar to advanced melanoma. Limited disease can be effectively managed by complete excision, which may require local flap coverage or skin grafting. More advanced but localized disease may be managed with radiotherapy. These manoeuvres may control the local disease until there is progression elsewhere. A small group of patients have symptomatic and persistent, aggressive or increasing ITM, and it is this group, many of whom have been exposed to previous treatments including surgery, chemotherapy and radiotherapy, who can benefit from ILI.

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