Isolated Limb Perfusion for Melanoma

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25.1 Introduction

The technique of isolated limb perfusion, utilising an oxygenated extracorporeal circuit, was pioneered by Creech et al. at Tulane University, New Orleans, in 1957 [1]. A complete response was achieved in the 76-year-old male patient with extensive recurrent melanoma of his leg, and this lasted until he died at the age of 92. The advantage of this intriguing treatment modality is that a high dose of a cytostatic drug can be delivered to a tumour-bearing limb without the risk of systemic side effects. Isolated limb perfusion is a valuable therapeutic option in patients with an unresectable limb tumour and especially in lesions with a high tendency for locoregional recurrence, as is sometimes the case in melanoma [2].

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25.2   Perfusion Methodology

25.2.1 Technique

Isolation of the blood circuit of a limb is achieved by open access to the major artery and vein supplying the limb and by ligating the collateral vessels. A tourniquet is applied around the limb proximal to the region to be perfused in order to compress the smaller vessels in the muscles and subcutaneous tissues. After insertion of a catheter in the major artery and vein, the isolated limb is perfused by an extracorporeal circulation, oxygenated and propelled by a heart-lung machine (Fig. 25.1). The cytostatic drug is administered into this circuit. The priming volume of the extracorporeal circuit is about 750 ml and is composed of 300 ml autologous whole blood diluted with physiological electrolyte solution to a haematocrit of about 30 %. The autologous blood is taken from the venous catheter, just before the start of the isolation. The flow-driven extracorporeal circulation aims for the highest flow rate possible without increasing the venous pressure more than 10 cm above the starting point. The venous pressure in the limb can be monitored in a subcutaneous vein at the distal end of the extremity. Physiological blood gas values can be obtained with flow rates of 30–40 ml/min/l tissue [3].

Perfusion may be conducted in the lower limb at the external iliac level, at the femoral or popliteal level and in the upper limb at the axillary or brachial level. For
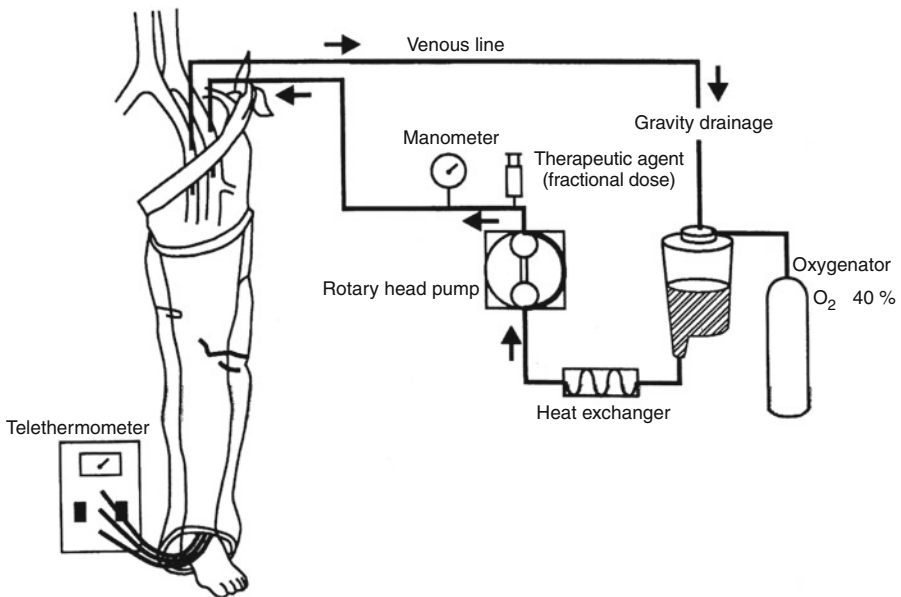

Fig. 25.1 Schematic drawing of the isolated perfusion circuit

iliac perfusion, the iliac and obturator lymph nodes are removed. Two recent descriptions of the surgical technique have been published [4, 5].

25.2.2 Drugs

Melphalan is the cytostatic drug of choice for melanoma. The dose of melphalan is guided by the limb volume to be perfused, and this volume can be determined by immersion of the limb in a cylinder filled with water [3]. The maximum dose associated with an acceptable risk of toxicity in the normal tissues is approximately 10 mg/l perfused tissue for the lower limb and 13 mg/l for the upper limb [6]. This difference in dosing is due to the change in drug concentration in the different circulating volumes that are used in upper and lower limb perfusions.

Recombinant tumour necrosis factor alpha (TNFα) is sometimes added to the melphalan in the circuit. The main indication for this biological response modifier is the presence of bulky, well-vascularised melanoma lesions, since TNFα has a selective destructive effect on newly formed vessels. This typically leads to thrombosis with acute necrosis of tumour tissue and to a selectively increased melphalan concentration in tumour tissue due to an enhanced permeability of the vessel walls [7–9]. Objective response data using other drugs like actinomycin D, cisplatin, vindesine, DTIC, fotemustine, interleukin-2 and lymphokine-activated killer cells are not encouraging [10–14]. It appears that none of these drugs is as effective as melphalan, neither as single agents nor in combination with other agents.

25.2.3 Monitoring Leakage

The extremely high cytostatic drug dosages in the limb could be fatal when they reach vital organs. The limbs, for example, can endure melphalan concentrations up to 20 times higher than would be tolerated in the rest of the body [6]. The potential leakage into the systemic circulation thus requires careful monitoring. To this end, a small dose of a radiopharmaceutical is administered into the extracorporeal circuit, and a detector placed over the heart registers radioactivity that reaches the main circulation. An experienced team can generally keep the leakage rate below 5 %. In 438 procedures, we measured a mean cumulative systemic leakage of 0.9 % (range 0.0–15.6 %) after 60 min of perfusion [15].

25.2.4 Tissue Temperatures

As we aim for physiological conditions, concentrating only on drug effectiveness, tissue temperatures of the limb are kept at normothermic levels between 37 and 38 °C during the whole drug circulation time. This is called "controlled" normothermia because special measures such as warming the perfusate and applying a warm water blanket around the limb must be taken to prevent the limb from cooling down

during the preparative surgery [2].The drug is added to the perfusate when a temperature of 37 °C is indicated by all four temperature probes inserted into proximal and distal subcutis and muscle. We question the benefit of the widely used so-called "mild" hyperthermia method (with tissue temperatures between 39 and 40 °C), since the specific cell-killing effect of heat is mainly obtained at temperatures exceeding 41.5 °C [16]. A retrospective analysis showed similar results for perfusions with normothermia and perfusions with mild hyperthermia [17]. "True" hyperthermia means heating the tissues to temperatures between 41.5 and 43 °C. Such high temperatures are no longer applied in perfusion because of unacceptable potentiation of melphalan toxicity by heat, although encouraging antitumour effects have been obtained [18]. The administration of true hyperthermia by a perfusion without cytostatics is, however, an option. Such a perfusion is based only on the cell-killing effect of high-dose hyperthermia [19]. To exploit this option, a double perfusion schedule was tested in our institute. A 2-h true hyperthermic (tissue temperatures between 42 and 43 °C) perfusion without melphalan was followed 1 week later by a 1-h normothermic perfusion with melphalan at a dose of 10 mg/l tissue [20]. The intention of the perfusion with high-dose hyperthermia was to kill cells in the hypoxic parts of the tumour, and the normothermic perfusion with high-dose melphalan was given to attack the residual well-perfused part of the tumour [21]. With this sequential schedule, both treatment modalities, high-dose hyperthermia and high-dose cytostatic, were given at their maximum dosage without an increase in toxicity, which the heat would have caused if used simultaneously with melphalan. Using this schedule, a high complete response rate (63 %) and a low limb recurrence rate (27 %) were seen in 17 patients with extensive, recurrent melanoma [22]. Toxicity was only mild. This regimen could be an alternative to perfusion with the combination of melphalan and TNFα in patients with extensive or bulky lesions.

25.3   Toxicity and Morbidity

25.3.1 Regional

Acute regional toxicity after isolated limb perfusion typically consists of slight oedema, erythema, and pain in a warm limb, commonly developing within 48 h after the procedure and resolving within 14 days (Fig. 25.2). The redness fades to a brown hue that gradually fades over a period of 3–6 months. Usually there is no visible evidence of any change after approximately 6 months. Other local manifestations are sometimes seen (e.g. temporary loss of nails (Fig. 25.3), drying or blistering of skin of the palm of the hand or sole of the foot, inhibition of hair growth on the extremity or transient neuralgia), but all subside over time. More severe toxicity may occur in the form of blistering and muscle damage. Damage to the deep tissues can cause permanent loss of function and may also result in a threatening or manifest compartment syndrome, which necessitates amputation on rare occasions. The grading system of these toxic reactions of the normal tissues after perfusion

Fig. 25.2 Normal acute regional toxicity reaction after isolated limb perfusion (Grade II) (Reproduced from the Textbook of Melanoma, 2004, with permission of Taylor and Francis [86])

with melphalan was introduced by Wieberdink et al. in 1982 (Table 25.1) [3]. From published data of large series, one can conclude that moderate to severe acute skin or soft tissue reactions (grades III–V according to Wieberdink) occur in 7–37 % of patients. The degree of acute regional injury has a significant effect on the incidence of long-term morbidity [23]. This long-term morbidity mainly consists of stiffness, muscle atrophy and functional impairment. Restricted range of ankle motion is seen in 25 % of the patients [24–26]. Severe chronic pain as a result of the procedure is reported in 5–8 % of the patients [23, 26]. The occurrence of long-term neuropathy was studied at the authors' institute and was encountered in 20 % of the patients after perfusion at the axillary level and in 2 % after perfusion at the iliac level [27]. This morbidity is usually the result of the tourniquet being applied too tight during the procedure. The most important risk factors for severe acute regional toxicity are tissue temperatures over 40 °C, a high melphalan peak concentration in the perfusate, female gender and obesity [18, 28]. The reason why obese extremities are prone to develop toxicity is the higher melphalan uptake in muscle compared to fat.

Fig. 25.3 Normal acute regional toxicity reaction (Grade II) with loss of nails

Table 25.1 Acute regional toxicity grading system according to Wieberdink et al. [3]

Grade I	No reaction
Grade II	Slight erythema and/or oedema
Grade III	Considerable erythema and/or oedema with some blistering; slightly disturbed motility permissible
Grade IV	Extensive epidermolysis and/or obvious damage to the deep tissues, causing definitive functional disturbances; threatening or manifest compartment syndrome
Grade V	Reaction which may necessitate amputation

Because the melphalan dosage is based on limb volume, muscle tissue in obese extremities is thus exposed to a relatively high drug dose [29]. Some strategies to lower the toxic reactions have been recommended. The melphalan peak concentration can be lowered without decreasing the absolute drug dose by using a larger priming volume and by prolonged or fractionated administration [30, 31]. Obese people often receive a 10 % reduction in melphalan dose [27].

25.3.2 Systemic

Systemic toxicity should be absent or mild, when leakage from the isolated limb is adequately controlled. Careful ligation of collateral vessels, the avoidance of high flow rates and high venous pressures and a thorough wash-out of the isolated circuit at the end of the procedure are particularly important in this respect. With these precautions, systemic toxicity was found to be absent or mild in patients perfused at the authors' institute, both after perfusions with melphalan alone and after perfusions in which the combination with TNFα was used [32, 33].

In the melphalan-alone group, nausea and vomiting were the most frequently encountered side effects. Fever immediately following the operation was common if TNFα was added. A systemic inflammatory response syndrome with hypotension and respiratory distress, as reported by others [34], was not observed in our TNFα-perfused patients.

25.4   Indications and Results

25.4.1 Locally Advanced Melanoma

Isolated perfusion with melphalan is the treatment of choice for patients with locally unresectable melanoma of a limb (Figs. 25.4, 25.5 and 25.6). In the past, these patients frequently had to undergo amputation, a mutilation that is now seldom necessary [35]. When the lesions are bulky and well vascularised, high response rates have been reported when melphalan is combined with TNFα [36, 37]. In a recent preclinical study in mice, selective targeting of VE-cadherin was found to be one of the mechanisms in which TNFα destroys the integrity of the tumour vasculature [38]. In our hands, a complete response rate of 59 % could be obtained with the combination of melphalan and TNFα in a group of 130 patients with truly unresectable lesions (i.e. more than ten nodules or nodules with a size larger than 3 cm) [39]. With melphalan alone, the complete response rate was 45 %. Approximately half of the patients with a complete response recurred in the perfused region after a median interval of 6 months after treatment. The recurrences could be managed by simple local treatment modalities, such as excision,
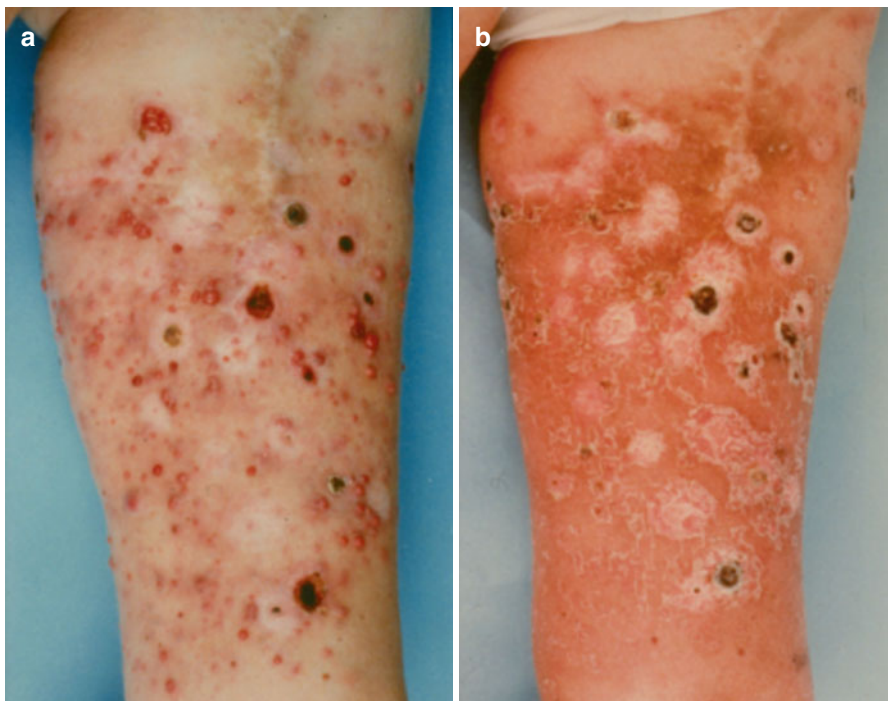

Fig. 25.4 (**a**) Multiple in-transit metastases of the left thigh. (**b**) Ongoing remission, 6 weeks after perfusion with melphalan. Complete remission was achieved some weeks later (Reproduced from the Textbook of Melanoma, 2004, with permission of Taylor and Francis [86])
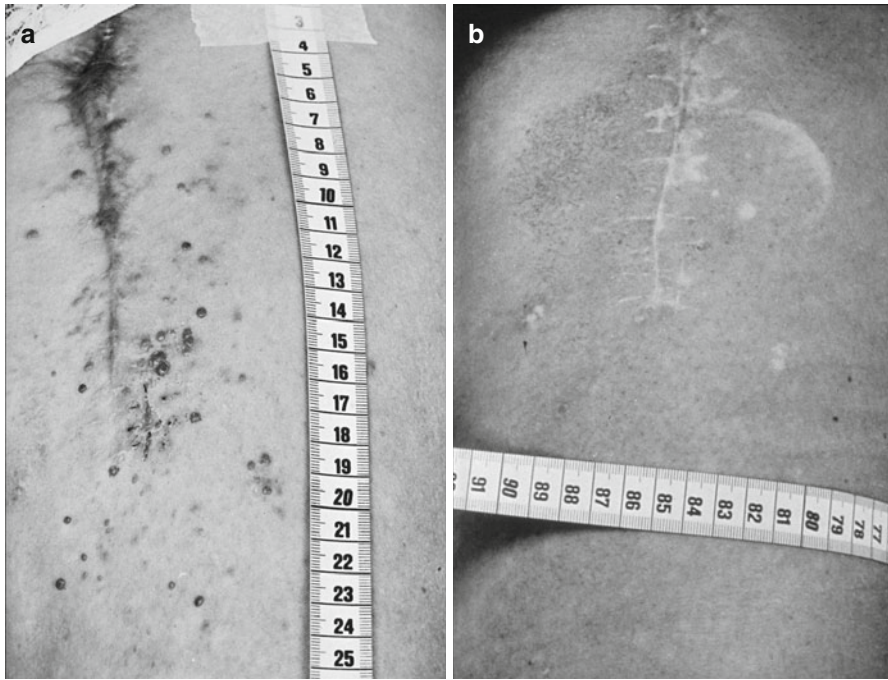
Fig. 25.5 (**a**) Multiple in-transit metastases around the scar of a left inguinal lymph node dissection. (**b**) Complete remission 3 months after perfusion

laser ablation or radiotherapy in 70 % of the patients. Approximately 50 % of the patients without a complete response could also be managed by simple local limb-sparing treatment. The limb-saving rate in the study population was 97 %, a satisfying percentage considering the fact that the disease had been truly unresectable in all cases. Literature shows the complete response rate after melphalan-alone perfusions for advanced limb melanoma to be on average 54 %, which is higher than the 45 % at our institution [40, 41]. This difference can be explained by a difference in tumour load. It has been shown that the number of lesions and the total tumour surface area are important prognostic factors for response after isolated limb perfusion [42, 43]. The published, complete response rates after isolated limb perfusion with the drug combination vary from 26 % to 90 %, with the higher percentages probably being attributable to a generally lower tumour load [37, 44–49]. In patients with a complete response, other investigators found subsequent limb recurrence rates comparable to ours: 44 % of the patients recur after a median interval of 5–10 months [40].

Perfusion may also be applied in the presence of distant melanoma metastases. Unresectable symptomatic locoregional limb melanoma is rare in these patients, but if present, perfusion can achieve satisfactory palliation [49]. The procedure has to be considered, especially in patients with distant skin metastases, distant subcutaneous metastases or distant nodal metastases, since these patients tend to survive longer than a year.

Fig. 25.6 (**a**) Neglected primary melanoma with bone involvement. (**b**) Complete remission 6 months after perfusion (Reproduced from the Textbook of Melanoma, 2004, with permission of Taylor and Francis [86])

A potential drawback of perfusion is the fact that it cannot be repeated frequently due to technical reasons. Still, a double perfusion schedule with intervals of 3–4 weeks between the treatments is feasible and has been investigated at the authors' institute [50]. Although 77 % of these patients obtained a complete response using such a schedule, half of them recurred in the perfused area after a median period of 5 months. It is noteworthy that in this study patients with a complete response had a significantly shorter time interval between their perfusions than patients without a complete response.

25.4.2 Isolated Limb Perfusion as an Adjunct in Primary and Recurrent Melanoma

Isolated limb perfusion as an adjunct after excision of high-risk primary melanoma (Breslow thickness $\geq$1.5 mm) was studied in a large multicentre randomised clinical trial, comprising 852 patients. The patients underwent either wide local excision or wide local excision and perfusion [51]. Locoregional recurrences occurred less frequently in the perfusion group (3.3 % versus 6.6 %, $P = 0.05$). The disease-free survival was better in the perfusion group during the first 2–3 years after treatment ($P = 0.02$), but no long-term effect was observed. There was no beneficial effect of perfusion on overall survival.

There is only one randomised prospective isolated limb perfusion study in patients with resectable recurrent melanoma [52]. In this rather small study, 69 patients with local recurrences, satellites and/or in-transit metastases were randomised to excision only or excision combined with perfusion. In the perfusion group, a lower locoregional recurrence rate of 45 % was seen versus 67 % in the excision-only group ($P=0.13$). The median disease-free interval was prolonged to 17 months after perfusion compared with 10 months after excision only ($P=0.04$). No significant difference in overall survival was observed, with 5-year survival rates of 44 % and 39 %, respectively ($P=0.28$).

The investigators of both studies concluded that isolated limb perfusion with all its costs and associated morbidity cannot be recommended as an adjunct treatment option, because no overall survival benefit was observed., However, it is interesting that perfusion reduced the number of recurrences and increased disease-free survival in both studies, suggesting a destructive effect on micrometastastic disease. Adjuvant perfusion may thus provide valuable locoregional disease control in patients with frequently recurring and multiple resectable lesions. This hypothesis was tested at the authors' institute in 43 patients, who had their first perfusion for a third or subsequent limb recurrence [53]. The median limb recurrence-free interval in these patients had decreased significantly over time from the primary excision to the third or fourth limb recurrence, for which perfusion was performed ($P<0.001$). After perfusion, the median limb recurrence-free interval was 4.7 times longer compared with the last interval before perfusion ($P<0.001$). The mean number of lesions was 2.6-fold lower compared with patients before perfusion ($P<0.001$). Perfusion in this study thus lengthened the limb recurrence-free interval and decreased the number of recurrences significantly. We concluded that perfusion is a valuable adjunct to excisional surgery of repeated locoregional melanoma recurrences in patients whose limb recurrence-free intervals tend to shorten over time [53].

25.5   Repeat Isolated Limb Perfusion

After successful treatment of locoregionally recurrent limb melanoma with isolated perfusion, further recurrences develop in 46–54 % of patients [54]. Treatment options in these situations vary depending on the extent of the disease and consist among others of further excision, CO_2 laser ablation, [55] intra-lesional chemo- or immunoablation, [56] and radiotherapy with or without local hyperthermia [57]. If lesions are too large or too numerous, repeat perfusion seems the only alternative to amputation. In 1996 the authors published their results of repeat isolated limb perfusion with melphalan, using various schedules, both single and multiple, normothermic and hyperthermic (tissue temperatures over 41.5 °C) [58]. A high complete response rate was obtained (74 %) with a limb recurrence-free interval of 9 months. The associated regional toxicity was substantial and was explained by the use of intensive schedules. Data on repeat perfusion using the combination of melphalan

and TNFα were published in 2006 [59]. The complete response rate was 62 %, and the median limb recurrence-free survival was 13 months. Regional toxicity was mild and comparable with the first perfusion, a finding that was also reported by others [60]. Repeat isolated limb perfusion with melphalan and TNFα seems feasible with a relatively high complete response rate, a considerable limb recurrence-free survival and mild regional toxicity.

25.6 Isolated Limb Perfusion in Elderly Patients

The mean life expectancy at age 75 is 8.5 years for males and 11 years for females [61]. Maintaining and improving the quality of life in this age group is desirable. Therefore, effective perfusion with low morbidity is important also in this phase of life. A study of 202 patients was performed combining data from the authors' institute and from Erasmus Medical Center–Daniel den Hoed Cancer Center, Rotterdam, the Netherlands. Toxicity, complications and long-term morbidity were similar in patients younger than 75 years of age and patients over 75 years of age [62]. Responses were also similar with 56 % complete responses in the older patients and 58 % complete responses in the younger patients. Hospital stay was somewhat longer in the older patients. Approximately half of the patients with a complete response achieved long-term locoregional disease control in either age category. It was concluded that older patients can undergo perfusion safely and derive the same benefit as younger people. Age is not a contraindication for isolated limb perfusion.

25.7 Prognostic Factors for Poor Survival After Perfusion

Patients with recurrent melanoma have 5-year survival rates varying between 27 and 56 %. Some of these patients do not survive longer than 1 year after treatment. Considering the usual 3–6 months duration of locoregional toxicity after perfusion and the maximum response of the lesions at a median of 4 months after the procedure, identification of a tool to select patients who will live long enough to experience the benefits of perfusion would be desirable.

In an attempt to identify prognostic factors for short survival, a study was performed in 439 patients with recurrent melanoma at our institute [63]. Sixty-nine of them (16 %) died within 1 year, 64 of metastatic melanoma. Patients with regional lymph node metastases or with regional lymph node metastases combined with satellites and/or in-transit metastases had a relative risk of 4.6 (95 % CI 2.0–6.6) and 3.6 (95 % CI 2.1–10) of dying within 1 year from perfusion, respectively ($p < 0.001$). In patients with distant disease, the relative risk was 22 (95 % CI 3.8–127, $p = 0.001$). Therefore, patients with limb melanoma have an increased risk of dying within 1 year after perfusion when regional lymph node or distant metastases are present. In these patients, the indication for perfusion should be carefully considered.

25.8   Quality of Life in Long-Term Survivors After Perfusion

Isolated limb perfusion can result in long-term morbidity in up to 40 % of the patients. We examined the impact of long-term morbidity on the quality of life. Fifty-one long-term disease-free survivors, perfused for recurrent melanoma (mean age 71 (38–90), median time after perfusion 14 (3–25) years), were selected from our database [64]. Quality of life assessment in this group was compared with an age- and gender-matched group of the Dutch population. It was demonstrated that the study group scored better on all domains of quality of life. The difference was statistically significant regarding bodily pain, general health perception, and overall mental and physical health scores. Nevertheless, the perfused patients reported considerable disease- and treatment-related morbidity, fear of recurrent disease and cosmetic problems. This counterintuitive outcome can be due to the composition of the study group, a favourable selection of long-term survivors, and "response shift", meaning that patients have changed their perspectives over time and accommodated these to their complaints.

25.9   Isolated Limb Infusion as an Alternative to Isolated Limb Perfusion

Isolated limb *in*fusion was designed as a simplified and minimally invasive alternative to isolated limb perfusion [65]. Similar to isolated limb perfusion, it involves a method of vascular isolation to be able to distribute high concentrations of cytotoxic drugs to the extremity (Fig. 25.7).

During isolated limb infusion, arterial and venous access are obtained percutaneously using a standard Seldinger technique, obviating the need for an open surgical procedure [66]. Via the contralateral femoral artery and vein, the tips of the catheters are placed in the disease-bearing limb. In the operating room, the catheters are connected to an extracorporeal circuit primed with saline solution, incorporating a heat exchanger but no mechanical pump or oxygenator. In order to achieve reliable isolation, a pneumatic tourniquet is inflated proximally around the affected limb. A low blood flow can be achieved in this isolated circuit by repeated aspiration from the venous catheter and reinjection into the arterial catheter, using a syringe. This results in a lower blood flow compared to isolated limb perfusion (150–1,000 ml/min for isolated limb perfusion vs. 50–100 ml/min for isolated limb infusion). The lack of oxygenation during isolated limb infusion results in a hypoxic and acidotic environment, rendering the melphalan more potent [67]. Great care is given to heating the limb with the goal to raise the temperature to mild hyperthermia, which is achieved by a heat exchanger in the external circuit, a warm air blanket placed around the limb and a radiant heater placed above it. The cytotoxic drug combination of choice for isolated limb infusion is melphalan and actinomycin D [68]. A relatively short circulation time of 30 min is sufficient given the 15–20 min half-life of melphalan and the quick tissue absorption of both melphalan and actinomycin D [68–70]. Real-time leakage control of the cytotoxic drugs to the systemic

ISOLATED LIMB INFUSION CIRCUIT

Venous Catheter

Arterial Catheter

Circuit with Blood Warming Coil

Pneumatic Tourniquet

Catheter located in Main Limb Artery

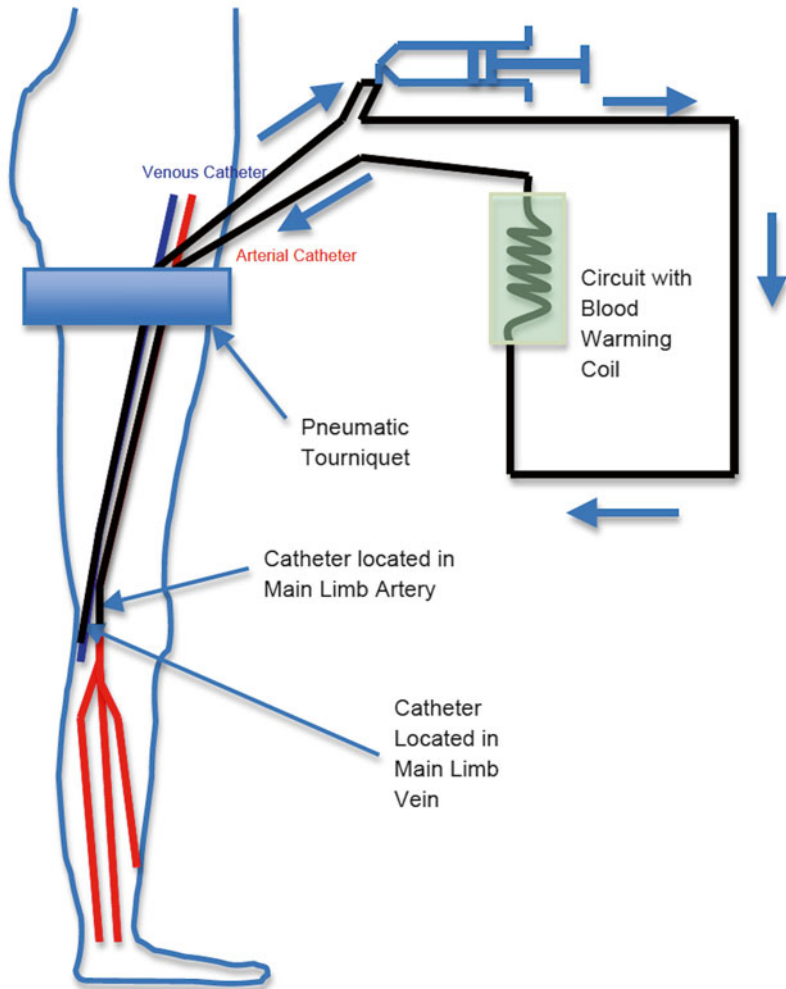Catheter Located in Main Limb Vein

Fig. 25.7 Schematic drawing of the isolated infusion circuit (Reproduced from Cancer Management and Research, 2013, with permission of Dove Press [87])

circulation is not required because the flow and the pressure in the isolated limb circuit are low and the pneumatic tourniquet secures effective isolation. After 30 min, the limb vasculature is flushed, and the normal circulation to the limb is restored by removing the tourniquet and the catheters.

Local toxicity following isolated limb infusion is also scored according to the Wieberdink classification [3]. On average, toxicity following infusion is limited and manageable [71]. A systematic review revealed that 2 % of the patients suffered from a threatening or manifest compartment syndrome after infusion [72]. Isolated

limb infusion can also safely be performed in elderly patients, and repeat procedures are possible without increased toxicity [73, 74].

Isolated infusion limb was pioneered at the Melanoma Institute Australia, and their response percentages appear somewhat less than those achieved by isolated limb perfusion, but this may be due to patient selection. Following isolated limb infusion, a complete response rate of 38 % and a partial response rate of 46 % are seen with a median duration of response of 22 and 13 months, respectively [75]. Recent reports from other centres show a somewhat lower fraction of responders [76, 77]. A multicenter US study achieved a 31 % complete response rate and a 33 % partial response rate [78]. Another multicenter study reported the responses in Australian centres, excluding the Melanoma Institute Australia. The complete response rate was 27 % and the partial response 36 % [79]. A recent systematic review including all original isolated limb infusion papers showed a complete response in 33 % of the patients and a partial response in 40 % [72]. Patient selection, slight technical differences and difficulties of standardising a response reporting system for in-transit metastases may play a role in the differences between the various reports [72, 80, 81]. Isolated limb infusion, for instance, is frequently performed in older and medically more compromised patients, both of which are statistically independent prognostic factors for an inferior response [75]. Similarly to isolated limb perfusion, isolated limb infusion does not alter survival as this is mostly dictated by tumour biology. Patients with a complete response to isolated limb infusion have a median survival of 53 months. Median survival times are significantly shorter in those with a partial response or stable disease [75]. More additional mature data from centres other than the Melanoma Institute Australia are needed to define the exact place of isolated limb infusion as a minimally invasive alternative procedure compared to isolated limb perfusion.

25.10 Future

Isolated limb perfusion has a significant effect on micrometastatic disease. Its application in resectable primary and recurrent melanoma lesions may therefore be useful. Tools to identify patients with a high risk of limb recurrence and a limited risk of distant metastases whose disease is susceptible to perfusion are desirable. Perhaps, genetic testing can select such patients. To lengthen the limb recurrence-free interval after perfusion, promising preliminary results of consolidation systemic biotherapy have been published. This combined regional and systemic approach deserves further study [82, 83].

Since 2010, a number of targeted systemic therapies and immunotherapies, such as B-Raf, MEK and KIT inhibitors, anti-CTLA4 antibodies and PD-1 pathway inhibitors, have become available and result in considerable response rates and improved survival in patients with inoperable stage III and IV melanoma [84]. Currently, however, the high 54 % complete response rate of perfusion and its modest morbidity compare favourably to the limited complete response rates and the substantial morbidity of these new drugs. We feel that perfusion (and infusion) is

still the first choice of treatment for patients with extensive disease confined to a limb [85]. For patients who also have distant metastases, systemic therapy with the new drugs may be a more attractive option. Combining systemic targeted therapy with high drug concentrations administered by isolated limb perfusion in these patients is another interesting option to be explored.

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