Regional Perfusion for Melanoma of the Extremities

Robert O. Pfefferkorn and Mukund S. Didolkar,
Department of Surgery
University of Maryland Hospital
Baltimore, Maryland

Abstract

A common cause for treatment failure in patients with malignant melanoma is local or regional recurrence of the disease. It is presumed that the poor treatment response rate is due to occult metastases present during the initial treatment phase. In an effort to improve response rate and survival, 15 patients with malignant melanoma of an extremity underwent isolated regional limb perfusion combined with hyperthermia and the cytotoxic drug Imidazole Carboxamide (DTIC). Study objectives include examination of response, subsequent tumor behavior after treatment, and the side effects of hyperthermia on the extremity. The 0-2 year response rate is 100%. None of the patients developed local recurrence, intransit or lymph node metastases, or disseminated tumor. There have been no surgical deaths and only a few patients developed some symptomatology of the known toxic side effects of the chemotherapeutic agent. Our early experience justifies the continued employment of regional hyperthermic chemotherapeutic isolation perfusion as an ideal treatment for patients who have malignant melanoma confined to an extremity.

Introduction

In the past, primary treatments for malignant melanoma of the extremities have been accompanied by high incidence of local or regional recurrence. This recurrence usually appears within 20–24 months after initial treatment. The manifestations are in the form of local recurrence, when the tumor nodule appears in the scar of the previous incision; satellitosis, when single or multiple tumor nodules occur within 3 cm distance of the previous excision site; intransit metastases, identifiable when the recurrent tumor nodules appear between 3 cm distance of the primary site and the regional lymph nodes. Prognosis of recurrent malignant melanoma is extremely grave. McNeer and Cantin reported a 20% 5-year survival rate.[1] Others have reported the survival rate to be as low as 14%.[2]

Treatment for both high risk and recurrent malignant melanoma of the extremity has included radical amputation, wide excision and systemic chemotherapy. Radical amputation of the extremity has been accompanied by a survival rate of 12% in patients who had positive regional lymph nodes and 34% in those with negative lymph nodes.[3] Overall survival figures from a variety of different series fall in 12–30% range indicating a poor result from such a radical approach.[4,1] Another highly recommended treatment has been wide re-excision of the locally recurring lesion. Frequently, however, these lesions are multiple with intransit metastases. Some are located subfascially which, combined with other factors, make it nearly impossible to achieve a successful wide excision of the tumor. Systemic chemotherapy, the third modality, has been used extensively for the treatment of advanced malignant melanomas. When used with various drugs or drug com-

Requests for Reprints to: Robert O. Pfefferkorn, C.C.P., Cardio-Sciences, Inc., 2500 Townsgate Road, Suite E, Westlake Village, CA 91361.

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binations, the response rates have been in the range of 15–40%.[5–8] The side effects of systemic chemotherapy, however, are usually pronounced and can be expected in greater than 60% of the patients treated.

An ideal treatment for patients who have malignant disease confined to an extremity is regional chemotherapeutic isolation perfusion. This modality has been in use since Creech and his associates introduced it in 1957.[9] The aim of isolated regional chemotherapy is to achieve a high drug concentration in the target tissue thus maximizing tumor cell kill without producing the serious side effects of systemic toxicity in those organs not affected by the cancer. The response rates for this method have been reported to be as high as 60–80% with excellent prolongation of survival.[10,11] When hyperthermia is combined with isolation perfusion, there is even greater cell kill and better results are thus achieved. The primary benefits of hyperthermia are that it (1) increases the binding rate of long-acting alkylating chemotherapeutic agents and, (2) increases the degree of vasodilatation allowing for greater exposure of the tumor to the circulating drug. In one reported series, the 5-year survival for locally recurrent malignant melanoma after hyperthermic isolation perfusion was 48.2% as compared with 20–34% after conventional surgical excision.[10]

A number of drugs including Melphalan, Actinomycin, Nitrogen Mustard, and Thio-tepa have been used for isolation perfusion chemotherapy. Melphalan has been most widely used as it appeared to be the most active of all in treating a malignant melanoma. Recently, however, Imidazole Carboxamide (DTIC)[a] has shown to provide the highest response rate when used for either systemic intra-venous or intra-arterial infusion.[12,13] Although the exact mechanism of DTIC's action is unknown, it is thought to inhibit DNA synthesis by acting as a purine analog. This eventually causes cell death by interfering with DNA's role in cell replication. It is also thought to be an alkylating agent which attacks a purine base in the DNA structure. DTIC safely lends itself to hyperthermic techniques as it is stable at temperatures up to 42 degrees C. The rate of decrease in DTIC concentration is approximately 2% per hour over three consecutive hours and the plasma half-life after I.V. administration is approximately 19 minutes.[14] Symptoms of anorexia, nausea, and vomiting are the most frequent toxic reactions with hemopoietic depression of leukocytes and platelets, the least experienced, but most severe of reactions. The recommended dose is 250 mg/m2/day I.V. for five days for systemic therapies. In our study, the dose was initially calculated at 600 mg/m^2 and now approximates 2 gm/m^2. Because this concentration is nearly eight times the systemic dose, the perfused extremity must be washed out with dextran and saline at the end of the procedure to avoid systemic toxicity.

Materials and Methods

After the patient is anesthetized, a surgical prep is performed to include the entire limb, chest, and shoulder for upper extremity perfusions and the limb, abdomen, and gluteal area for lower extremity perfusions. For upper extremities, radical axillary lymph node dissection is performed before the perfusion if it has not already been done. For lower extremity perfusions, the external iliac vessels are explored and the common and external lymph nodes are biopsied. In the lower extremity, the external iliac vessels are cannulated with a 12–16 Fr. arterial cannula and a 10–12 Fr. cannula is placed in the axillary vein for upper extremity perfusions. To check the proper placement of the arterial cannula, 10 cc of fluorescin dye is injected through the cannula and flow of the dye is followed with an ultra-violet lamp. Appearance of the dye in the distal arterial circulation within 20–30 seconds would indicate adequate placement of the arterial cannula.

The perfusion circuit consists of a Travenol low flow modular pump[b], 1/4'' I.D. arterial and venous tubing, a Bentley BOS-5[c] oxygenator and a Pall EC 1440[d] infant arterial line filter with filter bypass. A Harvey H 700 F[e] cardiotomy reservoir containing the washout solution is Y-connected to the arterial line on the negative side of the pump head to control the rate of washout infusion at the end of the procedure. 100% oxygen and 100% carbon dioxide gases are blended to achieve arterial

[a] Dome Div., Miles Laboratories, West Haven, CT 06516

[b] Travenol Laboratories, Deerfield, IL 60015

[c] Bentley Laboratories, Inc., Irvine, CA 92714

[d] Pall Bio-Medical Products, Glen Cove, NY 11542

[e] Bard Cardiopulmonary, Santa Ana, CA 92700

TABLE 1
Sex/Extremity Distribution

	No.	%
Males		
Upper Extremity	2	13
Lower Extremity	4	27
Females		
Upper Extremity	1	27
Lower Extremity	8	53
Total	15	100

pO_2's in the 250–400 mmHg range and arterial pCO_2's in the 45–50 mmHg range. A Sarns Heater-Cooler[f] is used to elevate the perfusate temperature and the limb is wrapped with a sterile warming pad to reduce external heat loss. The circuit is primed with 1,000 ml of balanced electrolyte solution and 3,000 units of sodium heparin. The patient is heparinized systemically with 10–12,000 units. A large rubber tourniquet, secured by a Steinman's pin placed at a 45 degree angle in the iliac crest, isolates the lower limb. For upper extremities, the tourniquet is wrapped around the shoulder area.

Water temperature and arterial blood temperature are monitored every two minutes. Additionally, the upper and lower deep muscle and the upper and lower skin surface temperatures of the isolated extremity are monitored with disposable probes at the same frequency. After checking the adequacy of venous return at the onset of bypass, the temperature of the perfusate is raised to 42 degrees C so that within 30 minutes, the temperature of the skin and the core of the extremity (calf or forearm muscle) will rise to 38–40 degrees C. When the temperatures have risen to expected levels and the venous return is balanced with the arterial input, 600 mg aliquots of DTIC are injected into the venous circuit at 5 minute intervals until the total calculated dose has been given. Perfusion is done for a minimum of one hour after the first aliquot has been administered. Flow rates of 150–250 ml/minute for the lower extremities and 75–125 ml/minute for the upper extremities are maintained. At the end of the perfusion, the limb is washed out with a mixture of 1,000 ml of normal saline and 1,000 ml Dextran 40 until a reduced hemoglobin level is visualized in the venous line (i.e. the perfusate becomes almost clear). The exact volume of priming and washout solutions are calculated and subtracted from the total amount of perfusate remaining in the oxygenator reservoir at the end of the procedure. Any imbalance can then be accounted for in both the immediate and postoperative management of the patient's fluid needs.

TABLE 2
Age/Physical Profile Distribution

	Age (Yrs)	Height (cm)	Weight (Kg)	B.S.A. (m2)
Mean	57.6	164.3	65.6	1.75
Range	30–82	155–180	50–100	1.55–2.02

[f] Sarns, Inc., Ann Arbor, MI 48103

TABLE 3
Blood Flow Rates

	Range	Mean
Upper Extremities	80–133 ml/min	107 ml/min
Lower Extremities	150–240 ml/min	208 ml/min

Results

From May, 1980 to September, 1981, 15 patients with Clark's Level III, IV, and V malignant melanoma of the extremity were treated by wide excision of the tumor and hyperthermic isolation perfusion chemotherapy with DTIC. There were 6 males and 9 females in this series (Table I). The distributions according to age and physical profile are shown in Table II. There were no deaths and only two patients developed complications of the procedure. One patient had a low WBC and platelet count probably as a result of incomplete washout of the drug. The second patient developed a deep vein thrombosis. No other complication, such as arterial thrombosis, peripheral neuritis, paralysis, atrophy or sloughing has been noted.

TABLE 4
Post-Bypass Fluid Balance

	Range	Mean
Upper Extremities	30–400 ml	210 ml
Lower Extremities	0–600 ml	203 ml
RBC Transfusion	0–3 units	1.5 units

TABLE 5
Mean Temperatures (C)

	Water	Perfusate	Upper Muscle	Lower Muscle	Upper Skin	Lower Skin
Pre-Bypass	30	31.2	33.5	33.4	43.4	31.4
DTIC Perfusion	41.1	39.3	35.7	36.9	16.5	36.6

Mean flow rates of 107 ml/minute for upper extremity perfusion and 208 ml/minute for lower extremities are well within prescribed levels (Table III). Balance between arterial input and venous return has been easily achieved without the addition of fluids to the circuit indicating no loss of perfusate to the systemic circulation. The patient fluid loss to the pump post-bypass averaged 210 ml for upper extremities and 203 ml for lower extremities (Table IV). An average of 1.5 units of packed cells per patient were transfused in the immediate post-bypass period with 4 patients not requiring any transfusion.

The average length of perfusion was 71.6 minutes for upper extremities and 91.8 minutes for lower extremities. The time difference indicates the greater difficulty experienced in warming the lower limb to hyperthermic levels due to both larger surface areas and wound size. Mean temperatures are indicated in Table V. We have experienced some continual heat loss when blood comes into contact with the shell of the oxygenator inhibiting our ability to repeatedly achieve desired hyperthermic levels. Attempts to correct this have been made by using a heat lamp placed over the oxygenator. The limb ischemic times have averaged 104 minutes with the longest times being recorded for upper extremity perfusions due to the higher degree of difficulty in cannulating the small axillary vessel.

Initially, the calculated drug dose was 600 mg/m^2. Gradually, it has been increased to 2 gm/m^2. We have not noted any toxic side effects with the higher doses and continue to use them to achieve the highest possible response rate. The definition of response is shown in Table VI. The response to treatment thus far in all 15 patients is complete. None of the patients in the high risk (10) or recurrent disease (5) categories have shown any recurrent tumor. The median follow-up period for these two groups is 18 plus and 21 plus months respectively.

TABLE 6
Classification of Treatment Response

A. Complete	100% tumor regression; no new lesions
B. Partial	50% tumor regression
C. Static	50% tumor regression or 25% progression
D. Progression	50% tumor regression; new lesions
E. Mixed	combination of D and A, B, or C

Conclusion

We have presented our experience with 15 patients with malignant melanoma of an extremity. All 15 underwent wide excision with isolated regional limb perfusion combined with hyperthermia and Imidazole Carboxamide. We are not aware of any other Center using this chemotherapeutic agent in this manner. Although this series is too small to be of statistical significance, several observations are worth noting. First, all patients have achieved a complete response without localized recurrence to this treatment. No serious side effects of either hyperthermia or the drug have been noted thus qualifying this technique as safe. Finally, it appears that this therapy does prevent the recurrence of local, regional and lymph node tumor and should, therefore, be explored further in larger clinical trials.

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