Malignant Melanoma

Medical and Surgical Management

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MALIGNANT MELANOMA:
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Chapter 22

ARTERIAL INFUSION TECHNIQUES FOR MALIGNANT MELANOMA

K.R. Aigner and H. Müller

INTRODUCTION

Approximately 15 to 20 percent of melanoma patients will eventually exhibit systemic metastasis. The treatment for metastatic melanoma in general remains unsatisfactory. Systemic chemotherapy, at the cost of moderate to high toxicity, results in low-partial response. One of the reasons for low incidence of response to systemic chemotherapy is low-level drug delivery to target tissue when the chemotherapeutic agent is administered intravenously. A higher systemic dose is precluded due to accompanying severe toxicity. Clinical studies of isolated perfusion for melanomas of the extremities have demonstrated that a higher drug dose can result in high rate of complete response and subsequent cure in selected cases.

The possibility of increase in the drug delivered to target tissue through intra-arterial administration have been evaluated for a wide variety of cancers. Drugs with short half-life such as 5 FU will have advantage of higher delivery at first passage. Also, manipulation of the blood flow rate to the target tissue can result in significant increase in drug delivery. Intra-arterial chemotherapies have been used for the treatment of melanoma. This chapter reviews the method, drug schedule, and toxicity of intra-arterial administration of chemotherapy for the treatment of melanoma.

INDICATIONS FOR INTRA-ARTERIAL INFUSION

Similar to isolated limb perfusion, intra-arterial chemotherapy for melanoma is suitable for metastasis localized to anatomic areas with defined dominant blood supply. However, unlike isolated perfusion system, intra-arterial chemotherapy is an open circuit. Therefore, after first pass effect and benefit of higher drug delivery following reduction of blood flow with intra-arterial balloon or external tourniquet compression, unbound drug will mix with systemic circulation with potential for the systemic toxicity. This excess drug escape to the systemic circulation can be reduced by chemofiltration of the venous blood. Intra-arterial chemotherapy may be instituted in partially open circuits like chest wall, shoulder, hip, inguinal region, accessible through subclavian or iliac artery. Simultaneous chemofiltration can be instituted to reduce the systemic leak of the drug and immediate and cumulative systemic toxicity with filtration catheter in subclavian or iliac vein.[1,2]

TECHNIQUE FOR THE CHEMOFILTRATION

A double lumen filtration catheter (PfM cologne, FRG) is inserted via the saphenous or the femoral vein and the tip is positioned under x ray control to the point where the maximum drug concentration is expected. The procedure is performed under systemic heparinization using local or general anesthesia. The filtration catheter is then connected to a chemoprocessor or a simple filtration unit consisting of three roller pumps, a filter, and scales. Filtrate container and substitution solution bags are both placed on the scales where an equilibrium is maintained throughout the procedure (Fig. 22-1). Dependency on the individual drug or drug combinations, intra-arterial infusion of chemotherapeutics is given over 30 to 60 minutes and chemofiltration is usually maintained for 60 to 90 minutes until the filtrate amounts to at least 10 liters.

Results

Melanoma data obtained so far shows that local response is improved in some cases, but nevertheless results were not striking, since impressive immediate tumor necroses as in isolated perfusion were not observed. However, systemic toxicity and side effects were lower, indicating a potential benefit of filtration.

In melanoma there is a need for prolongation of the local exposure time at higher drug concentrations in order to overcome the baseline level of chemoresistance, and achieve results similar to the isolation perfusion system. This can be attained either by blood-flow reduction, by temporary arterial blocking, or venous outflow occlusion.

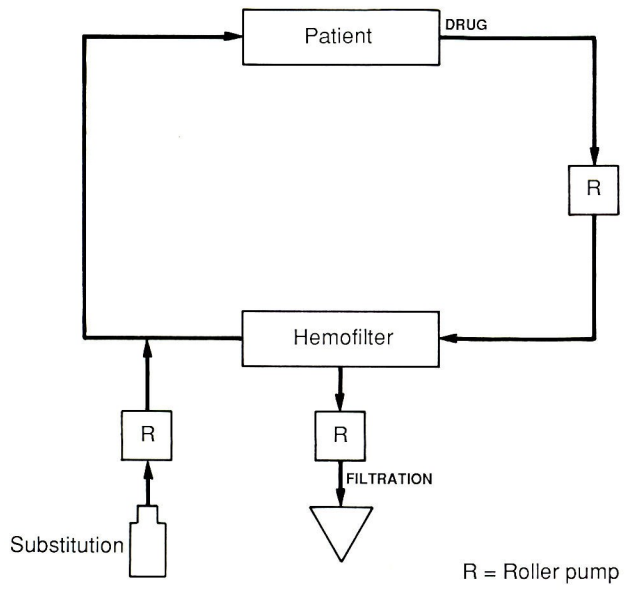

FIG. 22-1. Schematic illustration of chemofiltration.

CHEMOEMBOLIZATION

This method is suitable only for intra-arterial chemotherapy for liver metastasis especially from ocular melanoma. Chemoembolization combines temporary local ischemia and increase drug exposure, which results in an enhancement of cytotoxicity. Early experiences with Ethibloc®,[3] showed high morbidity and pain due to definitive blocking of capillary branches. Epidural anesthesia is mandatory when using Ethibloc®. Chemoembolization with Gel Foam® proved to be better in terms of morbidity and prevention of pain.

TECHNIQUE FOR CHEMOEMBOLIZATION

Vascular access may be achieved by means of an angiography catheter placed percutaneously through the femoral artery by the Seldinger technique with the tip of the catheter positioned into the common hepatic artery. Alternatively, surgical catheter placement may be performed with a routine technique using a port catheter (Jet Port II, PfM cologne, FRG) which tolerates high pressures in the port chamber as well as in the rigid polyurethane tube. The tip of the catheter is positioned and fixed in the gastroduodenal artery with its tip right at the origin from the common hepatic artery. The catheter is exited through the abdominal wall and connected to the port placed in a subcutaneous pouch on the fascia on the rectus abdominis muscle.

In order to keep side effects minimal, chemoembolization should be performed in three sittings on three consecutive days. For prophylaxis of pain just before each Gel Foam embolization, 3 to 5 ml of 0.5 percent Xylocaine is injected in 1 to 2 minutes through the arterial catheter.

In patients with average body weight of 70 kg, total doses of drugs for each cycle are calculated up to 20 mg of mitomycin C (MMC), 40 mg of melphalan (L-PAM) and 50 to 100 mg of Cisplatinin (CDDP). In case of extensive liver evolvement, MMC and L-PAM are reduced by 30 percent each. Daily doses do not exceed 10 mg of MMC, 20 mg of L-PAM, and 50 mg of CDDP. Combinations usually given are listed in Table 22-1. Embolisates consisting of 3 cm by 2 cm Gel Foam, 3 ml of 0.5 percent Xylocaine, and lyopholized drug injected over 3- to 5-minute period. This regimen is well tolerated by the patients. In general, epidural anesthesia is not necessary and remission induction usually can be seen in CT-scan a few days after the therapy showing hypodense metastases. Second look laparotomy, in case of marked response reveals tumor necrosis (Plates 58 and 59).

As mentioned previously, main indication for hepatic chemoembolization is metastases from ocu-

TABLE 22-1
DRUG DOSE AND SCHEDULE FOR HEPATIC CHEMOEMBOLIZATION

	MMC	L-PAM	CDDP	XYLOCAIN (1%)	GEL FOAM
Day 1	10 mg	20 mg		3 ml	3 cc
Day 2	10 mg		50 mg	3 ml	3 cc
Day 3		20 mg	50 mg	3 ml	3 cc

lar melanoma which has a tendency to metastasize predominantly to the liver. In most other anatomic areas of the body, however, chemoembolization cannot be applied due to excessive local ischemia. The appropriate technique to overcome this problem is reduction of the blood flow or complete blocking by means of tourniquet infusion.

TOURNIQUET INFUSION AND ARTERIAL BALLOON OCCLUSION

Both methods include temporary interruption of the arterial blood flow while the drug is injected into the main arterial vessel supplying a tumor-bearing limb or organ. The rationale are the local ischemia enhancing cytotoxicity of the drugs coupled with an increase in the local drug concentration resulting higher drug delivery due to low flow and low washout rate.

External Tourniquet Blocking

Although for advanced melanoma localized to the limb, isolation perfusion as described (see Chap. 19) is considered to be the treatment of choice, an effective alternative may be tourniquet infusion.[4–6] Duration of blocking can be chosen individually according to local tissue tolerance. This method is indicated for metastatic lesions in the limbs not reaching entirely up to the groin or axilla, since there must be some free space for the tourniquets such as inflatable cuffs or rubber bandages, placed as proximally as possible.

Arterial Balloon Catheter Occlusion

In contrast to the external tourniquet blocking method, this technique may be utilized for the lesions in the limb extending proximal to the inguinal ligament or the shoulder and also for lesion in the chest wall, pelvis, and lower abdominal area.

SUBCLAVIAN ARTERY INFUSION WITH BALLOON OCCLUSION

Presence of lesions in the axillary region and shoulder require placement of a balloon catheter into subclavian artery. Catheter is inserted by Sledinger technique from the groin and the tip is positioned distal to the origin of the vertebral artery to prevent infusion of the chemotherapeutic agents to the central nervous system. The balloon is then inflated and the blood flow through the subclavian artery is blocked. To verify correct positioning of the catheter, contrast imaging of all vascular branches is necessary (Plate 60). Homogeneous distribution of the drug to the target tissue is also checked by injection of blue dye through the catheter while the intra-arterial balloon is inflated (Plate 61). This procedure is considered mandatory to insure proper drug delivery to the target tissue since prior surgery and radiation therapy may alter the anatomic route of blood flow to the area of interest. Choice of the chemotherapeutics may be dictated by the protocol. We use single agent or combination of Melphalan, Cisplatinin, and Mitomycin C as described in the chemoembolization section (without Gel Foam). To avoid ischemic and vascular damage, occlusion time should not exceed 10 minutes. While catheter remains in place, it is connected to a perfusion pump with infusion of heparin at a rate of 20,000 unit per 24 hours. In responding patients where subsequent intra-arterial infusion for maintenance therapy is advisable, permanent port catheter may be implanted surgically. Through a supraclavicular incision, the subclavian artery is exposed, secured with a tape, and the tip of a jetport, all round catheter (PPM, cologne FRG) is inserted end-to-side in subclavian artery and fixed with a proline purse-string suture (Plate 62). The port is placed in a subcutaneous pouch on the pectoral muscle. This technique has been described. In order to achieve infusion in a more limited area, a pneumatic cuff is placed around the upper arm in order to stop the blood flow distally and preferentially infuse to the area supplied by axillary artery and to the chest wall.

ILIAC ARTERY BALLOON OCCLUSION

The technique for the iliac artery balloon occlusion for melanoma invading the groin or small pelvis is comparable to the subclavian access. Angiography catheters are introduced through the contralateral groin. The occlusion is achieved either in the common iliac artery or up in the aortic bifurcation. In case the diameter of the vessels is too large, one thin infusion catheter and one stronger blocking catheter are inserted simultaneously (Plate 63).

Depending on the location of the metastatic spread, blood flow to the distal limb can be blocked by means of a pneumatic cuff. Choice of drugs and their dosages are comparable to those for the subclavian infusion, however, they can be increased if the infused tissue volumes tend to be too large. As soon as the total doses reach or exceed systemically tolerable ranges, the addition of chemofiltration may be useful to prevent systemic toxicity.

DISCUSSION

Systemic chemotherapy for metastatic melanoma usually results in partial remission. Systemic toxicities limit use of higher dose of drug which would allow higher drug delivery to target tissue to improve response. Regional chemotherapy, as by administration of the drug by intra-arterial route, have several advantages. Tissue hypoxia, alteration of blood flow, drug exposure time, local hyperthermia, and so on, can all be utilized to improve drug delivery to tumor tissue to improve response. Intra-arterial administration of the drug for treatment of melanoma may be instituted using several different techniques such as chemoembolization, tourniquet infusion, or intra-arterial balloon occlusion. Each method has its own indication and advantages. Chemoembolization can only be used for melanoma in anatomic region which will tolerate embolization such as liver. Tourniquet infusion is applicable for lesions in the extremities not extending to inguinal region or shoulder area. For more proximal extremities lesions or lesions involving chest wall, gluteal region, and so forth, a balloon catheter occlusion chemoembolization technique is more applicable. This method can only be used for metastatic melanoma confined to an anatomic region which will tolerate embolism such as in liver. In the past decade, the techniques for chemoembolization were enveloped[3,7,8] and continuously improved by incorporation of results obtained from basic research.[9–11] To clinically exploit this concept of ischemia and prolonged drug exposure, it is important to optimize and standardize the method of chemoembolization as to make it easily feasible for the physicians and tolerable for the patients. Administration of total dose over 3 days is outlined in the protocol instead of single dose. Use of local anesthetics, and so on, decreased the morbidity significantly.

Intra-arterial administration with tourniquet infusion is an alternative to isolated perfusion. Similar to isolated perfusion, this method is suitable only for regional metastasis in the limb with disease limited below inguinal ligament or shoulder joint. However, this method may be utilized repeatedly without any antecedent surgical morbidity associated with isolation perfusion. The simplicity of the technique is its greatest advantage. This technique is also being improved continuously to achieve the best combination of occlusion time, extent of decrease of blood flow (complete vs. partial), and tissue tolerance.[4–6] Although it has been suggested that partial occlusion of blood flow may allow a more even distribution of the drug,[4] other investigators have showed fairly uniform drug distribution with both partial and complete occlusion.[6] We have shown that toxicity is not increased with 10 minutes occlusion compared to 5 minutes occlusion.[5] Yet, utilization of high-drug dose may necessitate reduction in occlusion time to avoid toxicity.

The technique of intra-arterial balloon occlusion can be utilized not only for melanoma confined to the extremities but also to disease extending more proximally to the chest wall and gluteal region and pelvis. In contrast to isolated perfusion, unbound drug administered by intra-arterial route will enter the systemic circulation and result in systemic toxicity. The possibility of these toxicity increase with utilization of higher drug dose. This systemic exposure to the drug can be effectively minimized by the use of the chemofiltration technique in conjunction with intra-arterial infusion.[3] Long-term control with improved survival as a result of intra-arterial infusion with blood-flow occlusion and reduction of systemic toxicity by concomitant use of hemefiltration needs to be studied in a prospective fashion.

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