Hyperthermic Isolated Limb Perfusion

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Abstract

In this overview we describe surgical procedures and hyperthermic-isolated limb perfusion techniques for the treatment of in transit metastases from melanoma and sarcoma of the limbs. We also briefly analyze the rationale of limb perfusion. The procedures are divided, for teaching purposes, in three phases (surgical procedure, perfusion time, reconstructive phase). Finally we present a brief summary of our results obtained in the treatment of sarcoma and melanoma. We have performed 91 limb perfusions on 86 patients (5 patients have been treated twice). We obtained an objective response on 93.6% of patients with in-transit metastases from melanoma (45.5% presented a complete response and 48.1% a partial response). About sarcoma of limbs, we reached an objective response on 80% of patients. Side effects have been mild and not life threatening (e.g., edema of the limb, leukopenia and a compartment syndrome).

Introduction and Indications of Limb Perfusion

The principles underlying the synergistic effects of cytostatic drugs and hyperthermia have been extensively described in previous chapters; briefly, we must emphasize that isolated limb perfusion offers two main pharmacokinetic advantages compared to systemic neoplastic treatment: (a) high drug concentration in the tumor area and (b) low systemic toxicity. Those important effects have been clinically applied initially for in-transit metastases from melanoma. In this condition, melanoma disseminates through the whole limb from the initial site to the regional lymph nodes. This situation is not easily managed with conventional surgical or chemotherapeutic treatments but is still a locally-advanced disease. Isolated limb perfusion achieves good survival and quality of life results without the toxic effects of systemic chemotherapy. Limb perfusion consists of three phases:

1. Surgical ablative phase (node dissection and vessel preparation)
2. Perfusion phase
3. Reconstructive phase

Basically, the treatment consists in isolating the limb from systemic circulation and perform limb perfusion with cytostatic drugs for 60 minutes with extracorporeal circulation (ECC) (Fig. 1).

At the beginning of the perfusion phase, blood in the limb is heated; when the tumor site and whole limb reach an homogeneous temperature of 41.3-41.5°C, the drugs are injected into the perfusion circuit at high concentration with low side effects for the rest of the body. The pharmacological benefit is linked not only to high concentration but also to a continuous circulation of drugs in the limb that increases the cytostatic uptake from tumor. As previously

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described, hyperthermia interacts with anticancer drugs at multiple levels. One direct effect is selective damage of tumor cells due to the decreased adaptability of tumor vessels to elevated temperature. This effect manifests as increased heat-entrapment in tumor areas compared to normal tissue, rendering hyperthermia a selective therapy. Another effect is related to increased permeability of tumor-cell membrane, induced by heat, that allows accumulation of drugs inside cancer cells. The intracellular concentration of drugs combined with heat shock causes impairment of DNA repair and disrupts DNA duplication. This action is especially marked in tumor cells which have a high proliferative index.

Hyperthermic isolated limb perfusion is indicated in following disease stages:
- treatment of in transit metastases from melanoma (Figs. 2, 3, 4)
- palliative treatment for melanoma when residual life quality is the target.
- curative treatment of soft tissue sarcomas
- limb-saving procedure and
- neoadjuvant treatment to reduce bulky tumors and allow successive conservative surgery.

Surgical Procedure

Ablative Phase

Lower Limbs

Iliac access is preferred for lower limbs. This access allows both iliac lymph node dissection and inguinal lymph no perfusion. Iliac node dissection is mandatory because in a non-negligible percentage of patients (30% in some studies) iliac-obturator lymph node disease can be present although the inguinal lymph nodes appear uninvolved. In selected cases (second perfusion or previous iliac lymphadenectomy), femoral access has to be utilized. Iliac access requires external iliac and obturator lymph node dissection with isolation of internal and external iliac vessels. Iliac perfusion, when groin lymphatic metastases are present, requires inguinal-crural and iliac-obturator nodes en-bloc dissection. In this case, wide incision must be done with section and reconstruction of the inguinal ligament. This perfusion access is accompanied by high morbidity (diastasis of wound margins, lymphorrhhea, wound