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REVIEW

Isolated pelvic perfusion in irradiated unresectable recurrence of pelvic tumor: Preliminary outcome and ongoing study

C. Uzan[a,*], D. Goere[a], F. Dumont[a], S. Gouy[a], J. Muret[b], A. Hakime[c], T. De Baere[c], S. Bonvalot[a]

[a] *Département de chirurgie, institut Gustave-Roussy, 114, rue Édouard-Vaillant, 94805 Villejuif, France*
[b] *Département d'anesthésie, institut Gustave-Roussy, 114, rue Édouard-Vaillant, 94805 Villejuif, France*
[c] *Département de radiologie interventionnelle, institut Gustave-Roussy, 114, rue Édouard-Vaillant, 94805 Villejuif, France*

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Summary The technique of isolated pelvic perfusion (IPP) using extracorporeal circulation is capable of delivering high dose chemotherapy in the pelvic cavity. This technique has improved over time, notably with the use of a G-suit placed and inflated above the iliac bifurcation to impede flow through percutaneous vascular routes. This approach is of potential value in patients with previously irradiated, locally advanced recurrences of cancer originating from the gynecological or gastrointestinal organs. Administration of tumor necrosis factor alpha (TNF-α) in combination with melphalan seems to provide response rates similar to those obtained in the technique of isolated extremity perfusion. A preliminary phase I study has shown promising results in terms of feasibility and response rates. A randomized study is currently underway to compare IPP to standard treatment in patients with unresectable recurrent pelvic tumors of gynecological or gastrointestinal origin.

Introduction

Locally advanced pelvic carcinomas and their parietal or presacral recurrences expose patients to mutilating surgery and sometimes pelvic exenterations [1]. In certain cases, surgery is either impossible or useless, leaving the patient prey to locally invasive disease. These local recurrences are rarely chemo-sensitive and usually occur in previously irradiated areas. Moreover, these same patients have almost always already undergone one or more regimens of chemotherapy. This has led to the idea of administering chemotherapy in high local concentrations using drugs capable of overcoming the chemo-resistance mechanism related to high interstitial pressure in these recurrent areas. In contrast to the technique of isolated extremity perfusion, however, isolated pelvic perfusion (IPP) is still in the domain of research, but remarkable advances having recently been made.

* Corresponding author.
E-mail address: catherine.uzan@igr.fr (C. Uzan).

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We present herein the results of a preliminary study, which is presently being completed by a phase III study.

Isolated extremity perfusions

The technique of isolated organ perfusions was developed in the 1960s [2], based on the technique of extracorporeal circulation (ECC) developed for cardiac surgery. Isolating an anatomical segment (extremity or organ) by extracorporeal circulation, followed by ''lavage'' before restoration of normal vascular circulation, allows the administration of high dose chemotherapy, 10 to 20 times superior to what is tolerable with systemic chemotherapy. This procedure is different from ''classical'' intra-arterial chemotherapy, which, while providing a concentration effect, does not allow delivery of doses higher than the maximal tolerable systemic dose. Effectively, despite ''first passage'' metabolism, much of the chemotherapy agent passes into the general circulation, and exposes the patient to systemic toxicity. As is the case with other types of surgery, isolated organ perfusions have progressed enormously in the last 40 years, particularly with the addition of hyperthermia [3], the simplification of circuits and novel percutaneous approaches. These successive improvements have enabled tumor necrosis factor alpha (TNF-α) to be safely administered.

TNF-α was discovered in 1975 [4]. Its principal usefulness as an adjunct in oncology derives from its ability to transform tumors into ''sponge-like'' tissue by decreasing the interstitial pressure, which is particularly elevated in radiated tissues, and by increasing the permeability of cell membranes to anti-mitotic drugs. Another mechanism of action is its anti-angiogenic activity resulting in necrosis of tumoral vessels [5—7]. These combined actions make TNF-α capable of reversing the tumor's resistance to certain anti-mitotic drugs by enhancing penetration of chemotherapy into sclerotic tissues and across the cell membrane.

Thus, the adjunctive use of TNF-α with anti-mitotic drugs administered via a loco-regional route has been developed in the treatment of metastatic sarcoma or in-transit metastatic melanoma. Although this technique allowed avoidance of amputations in some patients, the initial doses of TNF-α were elevated. Application of this technique in the extremities was difficult because of health care regulations and the risks related to extravasation of TNF-α.

Consequently, new studies have been performed using lower doses of TNF-α. In 2005 [8], smaller doses of TNF-α were found to be sufficient to provide complete response (CR) rates similar to high doses when used in combination with melphalan. The side effects of TNF-α extravasation at this lower dose were decreased allowing implementation of a less toxic regime with decreased risk. In this study, the rate of CR by radiologic criteria was 36% without a dose-response effect. The rates of histological CR (0% viable cells) and major response (less than 10% viable cells) were 13 and 14%, respectively. These results were confirmed by a second prospective study of 100 patients treated with 1 mg of TNF-α [9]. These reproducible outcomes have led to safer and less toxic regimens while reducing the costs.

Local extremity perfusion has become an effective option for in-transit melanoma metastases leading to objective response rates of approximately 70% using melphalan alone at a dose of 10 mg/L in the perfused limbs, while avoiding the neurotoxicity of other drugs [10]. Similarly, combined melphalan—TNF-α therapy in isolated extremity perfusion for sarcoma has led to CR rates of 30%, whereas melphalan alone is usually not effective in this histologic type of tumor. Because the combination of TNF-α with melphalan works effectively against the mechanism of resistance, this combination has gained use in other tumor models since this combination minimizes loco-regional toxicity level when administered via a loco-regional route.

Evolution of pelvic perfusion techniques and improvement of experimental isolated pelvic perfusion in the animal model

The pelvic ''stop-flow'' technique consists of cannulating the aorta and the vena cava above the iliac bifurcation [11]. Drug infusion using this setup allows concentration of the drug in the pelvic cavity but results in a high rate of systemic leakage via collateral vessels [12,13]. Several techniques have been developed to increase the concentration and the duration of contact [14].

One solution is to completely isolate the pelvis using extracorporeal circulation (ECC), extremity tourniquets and a G-suit inflated proximal to the aortic bifurcation. During experimental studies of isolated pelvic infusion in a calf model [15], placement of a G-suit above the aortic and caval cannulations decreased leakage from the perfusion area to the systemic compartment. The goal was to increase the concentration ratio between the pelvic area perfused under ECC and the systemic circulation. It was shown that the use of the G-suit was capable of significantly increasing drug exposure in the pelvic compartment when the ''stop-flow'' technique was used. This technical improvement allows use of this procedure for pelvic tumors in the male using low doses of TNF-α.

Isolated pelvic perfusion technique with G-suit in man

The technique combines the pelvic ''stop-flow'' setup with the use of a G-suit (Figs. 1 and 2). In our early experience, the cannulations were performed surgically; this approach was rapidly replaced by percutaneous cannulation, which is much simpler for the patient.

The first step consists of placement of a G-suit above the umbilicus, inflating it by increments of 50 mmHg under hemodynamic monitoring using esophageal Doppler or Swan-Ganz catheter (SvO_2 and continuous flow), with surveillance of peak pressures during ventilation. Tolerance testing of G-suit pressures is performed after induction of anesthesia and after optimization of vascular volume to determine the maximal level of inflation tolerated by the patient (hemodynamic and biologic tolerance criteria); the test is repeated after aorto-caval clamping and initiation of ECC to determine the maximal tolerable level of inflation under aorto-caval clamping at the time of injection of TNF-α.

The arterial and venous cannulations are performed using the Seldinger's technique: the right femoral arterial and left femoral vein are punctured percutaneously with an 18G intracath needle under ultrasound guidance. Introducers with backflow protectors are inserted over rigid guidewires and the occlusion balloons are then introduced under fluoroscopic control. The balloon sizes, varying from 13 to 33 mm, are selected according to the diameter of the distal aorta and the origin of the vena cava as evaluated on pre-operative imaging (MRI or CT scan). The venous return