

## Short Communication

# Isolated Perfusion Therapy for Advanced Cancers

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Patients with cancer require effective treatment, including surgical resection, radiotherapy, and chemotherapy, but only a few options are available for the treatment of advanced cancer. Intensive drug exposure is fundamental to the eradication of cancers. However, adverse effects often prevent the administration of sufficient doses, resulting in poor antitumor responses [1]. Theoretically, isolated regional perfusion chemotherapy is an attractive option with which to achieve better tumor exposure to any given agent and to avoid systemic toxicity by decreasing the degree of systemic drug exposure [2].

The first regional perfusion technique, introduced by Creech et al. [2], involved the use of an extracorporeal circuit to deliver a high concentration of drug to a regional arterial/venous circuit in an extremity. Over 5 decades of developments in regional therapeutic techniques, various regional techniques were devised for advanced cancers, including isolated pelvic perfusion (IPP), isolated hepatic perfusion (IHP), and renal tumor ablation with a closed renal circuit [3,4].

Two key issues need to be addressed for a successful perfusion technique. First, high drug concentrations are needed to eradicate cancers because a steep dose-response curve is the rule for most chemotherapeutic agents. For example, when cisplatin is used as an anticancer agent against gastrointestinal cancers, the mean reported half-maximal inhibitory concentration (IC50) values are 10.7 mg/L (standard deviation, 4.7 mg/L) for sensitive tumors and 71.2 mg/L (standard deviation, 47.2 mg/L) for resistant tumors [5]. The goal of successful antitumor chemotherapy is to provide a sufficient drug concentration that exceeds these IC50 values, particularly for drug-resistant tumors. Second, systemic toxicity should be avoided by decreasing the degree of systemic drug exposure.

IPP is associated with relatively high tissue drug exposure [6]; however, substantial drug leakage into systemic circulation via numerous venous and arterial collateral vessels in the pelvis limits the amount of anticancer agent that can be administered. The incidence of blood leakage from the pelvic region into systemic circulation during IPP ranges from 38% to 55% [7,8]. We developed a negative balance IPP (NIPP) technique, in which the volume withdrawn is increased to exceed the flow-in volume by using twin rotary pumps in order to decrease the pelvic venous blood pressure. This technique has been demonstrated to clearly reduce drug leakage into systemic circulation [9-11]. Since 1999, we have performed more than 400 sessions of NIPP

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in 250 patients with advanced pelvic cancers such as recurrent rectal cancer, invasive bladder cancer, uterine cancer, and recurrent ovarian cancer.

Surgical IHP has succeeded in limiting the systemic leakage rate to 0%–3% and has yielded promising results [12,13]. Despite the encouraging results, this technique is therapeutically limited because it requires aggressive surgical intervention and can be performed only once. Orthograde percutaneous IHP techniques that use balloon occlusion catheters were developed to achieve safe and repeatable IHP. However, these techniques are associated with higher rates of leakage from the perfusion circuit into systemic circulation [14,15]. These higher rates are mainly because the distance between right atrium and hepatic vein origins is often too short to allow balloon occlusion of the suprahepatic inferior vena cava (IVC) above the hepatic veins without occluding the hepatic veins themselves [14,15] and incompletely occluding the IVC or diaphragmatic veins. When segmental hepatic venous outflow is acutely occluded, the corresponding liver parenchyma is supplied only by the artery and drained via the portal vein [16,17], suggesting that percutaneous IHP could be applied by employing hepatic artery inflow and portal vein outflow. We used this theory to develop a percutaneous IHP circulation system, retrograde-outflow percutaneous IHP (R-PIHP), by redirecting hepatic outflow through the portal vein [18]. We have begun a phase I/II trial of R-PIHP for advanced liver malignancies. R-PIHP was successfully performed in 27 sessions in 13 patients without the occurrence of grade 3 or higher adverse events.

Finally, we are now taking on the challenge of improving the prognosis of patients with advanced pancreatic cancer and developing a percutaneous isolated pancreatic perfusion therapy. We hope that these results will be reported in the near future.

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