

Splenic artery infusion of IL-2 might allow treatment of melanoma and renal cell cancer with less side effects and greater efficacy

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Editorial

Intravenous administration of interleukin-2 (IL-2) is a useful therapy for stage IV melanoma and renal cell cancer, stimulating proliferation of T cells, lymphocyte activated killer cells, natural killer cells and other immune effectors, which then target and eliminate cancer cells. In about 15 % of patients, tumor burden is significantly lessened and complete cure is seen in 6 - 8 %.¹⁻³ However, IL-2 therapy can cause severe side effects including pulmonary edema, psychosis, renal failure, hepatitis and myocardial infarctions.³ The treatment protocols basically simulate septic shock to get an immune response against cancer. Patients have to pass a cardiac stress test before starting IL-2, and as a result many patients are precluded from even starting IL-2 therapy. Those medically cleared for the grueling protocol undergo intensive care level monitoring while receiving IL-2 infusions. Even for patients able to tolerate IL-2 therapy without permanent harm, almost always the number of doses given in any cycle is well below the optimal amount because of patients start showing unacceptable side effects. I personally have had the experience of patients experiencing severe shaking rigors, at the very threshold of threatened end organ damage, yet desperately pleading for just one more dose of IL-2, to get just that much more chance of disease-free survival. Those desperate patients prompt me to propose to this audience that we should consider reviving the old idea of administering IL-2 into the splenic artery instead of the systemic circulation.

The concept of splenic artery infusion of IL-2 for cancer immunotherapy goes back over a quarter of a century, but new efforts are needed. The basic premise, validated in data so far, is that you need far smaller amounts of intrasplenic-

ly infused IL-2 to get maximum immune response, and most, if not all, of the IL-2 has its action within the spleen rather than the systemic circulation. The spleen gives rise to 25 % of total circulating T lymphocytes and 10 - 15 % of B lymphocytes, and about 50 % of all lymphocytes in the body are thought to pass through the splenic arterioles in the course of their lifetime. The spleen receives 100 % of its arterial blood supply from the splenic artery, making percutaneous access relatively easy. Pilot testing of splenic artery infusion of IL-2 first took place in mouse models in the mid 1980's.⁴ Subsequently in 1990, 20 patients with stage IV renal cell cancer, melanoma and lymphoma underwent a phase I clinical trial with low dose IL-2 continuously infused over 5 consecutive days at 3 weeks intervals for 2 - 4 cycles via a splenic arterial catheter placed through the femoral artery.⁵ Each patient received from 90,000 - 240,000 IU/kg/day for a total dose of 450,000-1.2 million IU/kg/cycle, much lower than the maximum dose of 8.4 million IU/kg/cycle with current systemic IL-2. In 3 of the 20 patients, visible reduction of tumor burden could be demonstrated. Two patients with renal cell cancer had complete regression of hepatic metastases, while primary tumor and other extra-renal metastases were unchanged. A third patient one with non-Hodgkin's lymphoma, had 40 % reduction of total tumor within lymph nodes. All of the patients in the study had measurable increases in natural killer cells and lymphocyte activated killer cells, and none of the 20 patients had any known side effects.⁵

In addition to the above study, in the 1990's there were small open trials of splenic IL-2 for stage IV melanoma, colorectal cancer and pancreatic cancer metastatic to the liver; these protocols also gave IL-2 via the hepatic artery and some of them also gave other chemotherapy or infused activated natural cells back into the hepatic artery.⁶⁻¹³ Access of the splenic artery was surgical rather than percutaneous. In all of these trials there appeared to be clinical benefit without undue adverse reactions. To the best of my knowledge, these are the most recent clinical trials of splenic artery infusion of

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IL-2, but there have been more recent case reports of patients getting splenic artery infusion of chemotherapy for myelofibrosis¹⁴, which confirms that the technology for splenic artery infusion of IL-2 remains current.

Furthermore, in 1992 there was a published series of 51 patients who underwent splenic artery catheterization specifically to infuse IL-2, providing a benchmark of expected safety.¹⁵ In this series, the rate of complications from splenic artery catheterization was fairly low, with 4.5 % of patients having subintimal contrast injection, 2.3 % having bleeding and hematoma and with a mortality from the procedure of 0 % (one patient had cardiac arrest from IL-2 infusion rather than splenic artery catheterization and this patient was successfully resuscitated).¹⁵ The one limitation of this study is that patients received both splenic and intravenous infusions of IL-2 at different time points, and so patients too medically frail for intravenous IL-2 were not included. Still, it provides a useful guidepost for new research protocols.

I am working under the assumption that splenic artery IL-2 will be delivered via an indwelling percutaneous catheter placed by an interventional radiologist, rather than via surgical exposure of the splenic artery. The former is obviously less expensive, less invasive and requires much less time for recovery. An analogy is that patients who have percutaneous coronary angioplasty and stenting spend much less time in the hospital compared those who have coronary artery bypass grafting surgery. Moving forward, efficacy of splenic IL-2 should be confirmed both with animal models and clinical trials. An excellent model system for metastatic melanoma exists in the form of a strain of Sinclair swine that develop a hereditary metastatic melanoma.¹⁶⁻¹⁹ In 85-95 % of the melanoma bearing Sinclair swine, there is complete spontaneous regression of the melanomas by young adulthood (8 months old) through both immune mediated mechanisms as well as natural differentiation and preprogrammed apoptosis. Those pigs unable to clear melanoma on their own would be an ideal experimental system for infusing splenic IL-2. For clinical trials, a logical place to start would be with stage IV melanoma and renal cell cancer who are failing IL-2 protocols due to intolerance of side effects or lack of tumor regression. For both animal and clinical studies, the aim should be the same: quantitative proof that splenic artery IL-2 can achieve greater biological effect against metastatic stage IV cancer with less or no systemic side effects. For clinical trials, another important aim should be to prove that patients ineligible for systemic IL-2 due to medical comorbidities can tolerate splenic IL-2 infusions without problems.

Latter day success with splenic IL-2 could provide new options and better outcomes for patients with untreatable metastatic melanoma, renal cell cancer and other malignancies.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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