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Regional delivery of anticancer drugs: Current applications

ABSTRACT

For cancers that remain confined to a specific region through most of their course, one treatment option is to deliver anticancer drugs directly to that region. Clinical experience shows that regional delivery can palliate symptoms, improve quality of life, and prolong survival. However, whether it increases the cure rate remains controversial, and it is costly because of the need to surgically implant infusion devices.

KEY POINTS

Regional delivery can kill more tumor cells by exposing the tumor to higher concentrations of the anticancer drug than are possible with systemic delivery.

Regional delivery has been employed against ovarian cancer, colon cancer metastatic to the liver, metastatic melanoma confined to an extremity, meningeal carcinomatosis from leukemia and lymphoma, and localized cancers of the bladder.

REGIONAL DELIVERY of anticancer drugs (directly to the body area where the tumor is located) is now standard treatment in selected patients. It can significantly palliate symptoms, improve quality of life, and prolong survival.

This article reviews the rationale for regional delivery of anticancer drugs, the clinical settings in which it can be applied, its safety, and its cost.

'DOSE INTENSITY' IN CANCER MEDICINE

The goal of regional delivery is to make the treatment more effective by increasing the concentration of the anticancer agent in contact with the tumor—without increasing the toxic side effects.[1] Two decades of clinical experience, substantial preclinical data, and some clinical data show that, in certain cancers, delivering a higher concentration of drug to the tumor for a longer time can kill tumor cells better than systemic therapy.

Unfortunately, current anticancer drugs have a narrow therapeutic index. They can significantly suppress bone marrow activity (resulting in neutropenia, thrombocytopenia, and anemia); damage the kidney, liver, and peripheral nerves; and cause nausea, vomiting, and hair loss. Regional delivery, which involves higher concentrations of drug for longer periods, poses obvious safety concerns.

WHICH CANCERS RESPOND BEST TO REGIONAL DRUG DELIVERY?

Cancer specialists use the following criteria when deciding whether regional delivery is appropriate:

The cancer should be confined to the body compartment for all or most of its natural course. Examples include ovarian cancer confined to the peritoneal cavity, colon cancer metastatic to the liver, melanoma metastatic to a single extremity, meningeal carcinomatosis from leukemia and lymphoma, and localized cancers of the bladder.[2]

The area to be treated should be the site of the major morbidity or mortality from the disease. In the examples given above, controlling disease in the specific region involved with the malignancy can have a major impact on both the quality and quantity of life.

The body compartment can be safely isolated for regional drug delivery.

The treatment should be cost-effective.

WHAT MAKES A DRUG 'IDEAL' FOR REGIONAL DELIVERY?

Not all anticancer drugs can be used for regional delivery. The following characteristics make an anticancer drug ideal for regional delivery:

The drug must be active against the specific cancer in systemic therapy. Examples are cisplatin in ovarian cancer and 5-fluorouracil in colon cancer.

The drug should not cause serious local toxicity to the infused or perfused body compartment or blood vessel or to normal tissues exposed to the high drug concentrations (eg, the liver following hepatic arterial infusion).

The drug should be more effective in more-intense regimens. Preclinical data from in vitro or in vivo models should suggest that increasing the concentration of the drug or duration of its exposure to tumor cells increases the number of tumor cells killed. In addition, data from well-designed randomized trials of the drug in systemic treatment should indicate the importance of dose intensity. The argument is that any advantage of dose intensity demonstrated with systemic delivery can be magnified with the higher drug concentrations achievable with regional drug administration.

The drug should undergo rapid, first-pass hepatic metabolism to nontoxic metabolites if it is to be given via the intrahepatic artery or intraperitoneally. Since the liver is a major site of drug metabolism, this feature can significantly increase the degree of local tumor-drug interaction while reducing systemic exposure and toxicity.

Specific regimens

Regional delivery has been demonstrated to improve the quality of life, prolong the time to symptomatic disease progression, or prolong overall survival in the following clinical settings:

- Meningeal leukemia and lymphoma, treated with cytarabine or methotrexate injected intrathecally (through the theca of the spinal cord into the subarachnoid space) or into the ventricles of the brain
- Localized bladder cancer, treated with thiotepa, doxorubicin, mitomycin C, or bacillus Calmette-Guérin (BCG) instilled into the bladder
- Ovarian cancer, treated with cisplatin, paclitaxel, or interferon-alfa instilled into the peritoneal cavity
- Colon cancer metastasized to the liver, treated with 5-fluorouracil or floxuridine infused into the hepatic artery
- Metastatic melanoma confined to an extremity, treated with melphalan perfused into the femoral or brachial artery and removed from the corresponding vein before the drug enters the general systemic circulation.

Regional chemotherapy is beneficial, within strict criteria

PROBLEMS AND QUESTIONS

Clinical trials showed that regional delivery of anticancer drugs can produce objective improvements (eg, shrink tumor masses, reduce the rate of accumulation of malignant ascites, prolong survival) and subjective improvements (eg, reduce pain, dyspnea).[3–7] However, some areas need further investigation.

Long-term impact is uncertain

The ultimate impact of regional delivery of anticancer drugs on the cure rate remains uncertain because patients with advanced cancers frequently have multiple potential areas in which the tumor may have already spread. Therefore, even if the growth of the malignancy is controlled in one region, the

cancer can progress elsewhere. For example, a tumor may spread to the peritoneal cavity or regional lymph nodes despite successful intrahepatic arterial treatment of colon cancer metastatic to the liver.[3]

Costs remain high

Regional delivery of anticancer drugs remains expensive because of technical requirements,[2,4] such as the surgical implantation of infusion devices. More cost-effective methods of regional drug delivery need to be developed that will be acceptable to patients and physicians.

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