Regional Administration of Antineoplastic Drugs

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1. INTRODUCTION
Regional antineoplastic drug delivery is not a new concept. Following the initial recognition that cytotoxic alkylating agents could cause shrinkage of tumor masses and a reduction in the quantity of malignant ascites in patients with advanced ovarian cancer, investigators in the 1950s instilled the drugs directly into the peritoneal cavity in an effort to treat the malignancy (1).

Similarly, intrathecal administration of methotrexate in the treatment and prevention of meningeal leukemia (2), intravesical treatment of superficial bladder cancer (3), and direct administration of drugs into blood vessels feeding a localized cancer (4), have been evaluated for more than a decade as therapeutic strategies in the management of malignant disease.

In this chapter, the basic pharmacokinetic rationale supporting regional antineoplastic drug delivery will be presented, followed by a discussion of theoretical concerns and practical issues associated with this treatment approach. The chapter will conclude with several examples of regional antineoplastic therapy which have been accepted as “standard of care” in the management of certain clinical settings, and other more experimental strategies employing the regional route of drug delivery.

2. PHARMACOKINETIC RATIONALE
The basic aim of regional antineoplastic drug delivery is to deliver a higher concentration of the agent to the tumor present within a particular region of the body, and to
expose the tumor to the active drug for longer periods of time than are safely possible with systemic administration (5–9). A favorable pharmacokinetic advantage for exposure of the body compartment (e.g., peritoneal cavity, liver, bladder) compared to that of the systemic compartment can be measured by increases in the peak concentration of drug, a greater AUC (area-under-the-concentration-versus-time curve), or both (Table 1). The entire pharmacokinetic advantage associated with regional drug delivery occurs during the first pass of the agent through the area perfused or infused. Even if the drug subsequently reaches the tumor through the normal capillary flow into the area, there will be no additional pharmacokinetic benefit associated with this delivery compared to what would have been achieved following systemic administration of the agent.

2.1. Mathematical Model Describing Regional Antineoplastic Drug Delivery

It is possible to define the pharmacokinetic advantage resulting from regional drug delivery by comparing the amount of the agent gaining entry into the region following this method of administration to that achieved with systemic (generally intravenous) treatment (Table 2, Equation 1). A similar calculation can be derived for the relative reduction in systemic exposure associated with regional drug delivery by comparing the concentration of drug found in the systemic compartment after regional and systemic treatments (Table 2, Equation 2).

Combining these two calculations provides an estimate of the overall relative pharmacokinetic advantage resulting from the regional treatment strategy (Table 2, Equation 3).

2.2. Clinical Implications of the Model

Careful examination of Equation 3 (Table 2) leads to several important conclusions relevant to the clinical use of regional antineoplastic drug delivery (Table 3).

The relative pharmacokinetic advantage associated with regional drug administration will be enhanced by measures which either reduce the clearance of the agent from the region and/or increase the clearance from the systemic compartment. Examples of measures which have been employed in the clinical setting to enhance the pharmacokinetic advantage of regional drug delivery are briefly outlined in Table 3.

Analysis of the model leads to several additional implications. First, antineoplastic agents that are not able to be cleared rapidly from the systemic circulation following perfusion/infusion through a region (by first-pass metabolism or artificial removal) will be associated with a relatively less favorable pharmacokinetic advantage, compared to drugs that exhibit this characteristic. However, even in this circumstance there may be

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**Table 1**

Rationale for Regional Antineoplastic Drug Delivery

| 1. Higher peak levels of drug in contact with tumor in the region of the body infused/perfused (when compared with systemic compartment). |
| 2. Prolong exposure of tumor present within the region to antineoplastic drugs (particularly relevant for cycle-specific cytotoxic agents). |
| 3. Reduction in systemic toxicity. |
| 4. Improve opportunity to observe clinically relevant concentration-dependent synergy between antineoplastic agents. |
a valuable contribution associated with regional drug delivery, depending upon other clinical conditions, for example, inherently slow blood flow through a region or highly active cytotoxic drug in the tumor type being treated.

Second, whether the pharmacokinetic advantage associated with regional drug administration of a particular drug is great (e.g., > 100-fold), or relatively minor (e.g., 10-fold), will be only one factor in determining whether a regional treatment strategy is a reasonable therapeutic option in a particular clinical setting.

An important consideration is the actual antineoplastic effectiveness of the agent against the tumor type in question. The regional administration of a drug with a >1000-fold pharmacokinetic advantage (either in peak concentrations or AUC) will not convert a totally inactive drug against a particular tumor type into a useful therapeutic agent.

However, the modest or major increases in tumor–drug interactions possible with regional drug administration have the theoretical potential to result in enhanced cytotoxicity for agents whose activity is known to be concentration-dependent or cycle-specific (10,11). In certain clinical circumstances, regional drug delivery can increase both peak levels and duration of exposure far beyond what can be safely accomplished

### Table 2
**Pharmacokinetic Advantage Associated with Regional Antineoplastic Drug Delivery**

<table>
<thead>
<tr>
<th>Equation 1: Relative increase in exposure to infused/perfused region:</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_{\text{local}} = \frac{C_{\text{local (regional)}}}{C_{\text{local (IV)}}} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equation 2: Relative decrease in exposure to systemic compartment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_{\text{systemic}} = \frac{C_{\text{systemic (regional)}}}{C_{\text{systemic (IV)}}} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equation 3: Overall pharmacokinetic advantage associated with regional drug delivery:</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R = \frac{R_{\text{local}}}{R_{\text{systemic}}} = \frac{C_{\text{local (regional)}}}{C_{\text{local (IV)}}} \cdot \frac{C_{\text{systemic (regional)}}}{C_{\text{systemic (IV)}}} )</td>
</tr>
</tbody>
</table>

Code: \( R_{\text{local}} \) = relative increased exposure to infused/perfused region; \( R_{\text{systemic}} \) = relative decreased exposure to systemic compartment; \( C_{\text{local (regional)}} \) = local concentration following regional drug delivery; \( C_{\text{local (IV)}} \) = local concentration following systemic drug delivery; \( C_{\text{systemic (regional)}} \) = systemic concentration following local drug delivery; \( C_{\text{systemic (IV)}} \) = systemic concentration following systemic drug delivery; \( R \) = overall pharmacokinetic advantage associated with regional drug delivery.

### Table 3
**Opportunities to Improve the Pharmacokinetic Advantage Observed with Regional Antineoplastic Drug Delivery**

1. Removal of agent during first pass through perfused organ (e.g., hepatic artery infusion therapy for colon cancer metastatic to the liver).
2. Removal of agent after perfusion through the treated organ, but prior to entry into the systemic circulation (e.g., isolation-perfusion techniques for treating extremity melanomas).
3. Systemic administration of an antagonist for a cytotoxic agent delivered regionally, with the aim to neutralize the drug prior to the production systemic side effects (e.g., intravenous leucovorin following intrathecal methotrexate in the treatment of meningeal leukemia).
4. Use of materials to decrease rate of blood flow through the perfused organ and enhance drug removal (e.g., starch microspheres during hepatic artery infusion).
with systemic administration (8). Clinically relevant examples include: the intraperitoneal delivery of cisplatin in patients with ovarian cancer, which achieves a 20-fold increased exposure to the peritoneal cavity when compared with the systemic compartment (12,13), and hepatic artery infusion of floxuridine (FUDR®), which results in 15-fold higher tumor drug levels when compared to those levels resulting from portal vein infusion of the drug (14).

Because significant limitations of preclinical models in predicting activity of antineoplastic drugs in patients are well recognized, data demonstrating the relative importance of concentration and duration of exposure in model systems can be helpful in selecting drug(s) for inclusion in human trials of regional antineoplastic therapy (15). For example, if an in vitro model demonstrates that administering concentrations of drug “A” at levels 100 times higher than are achievable with systemic delivery will not produce a significantly greater degree of tumor cell kill, and the regional pharmacokinetic advantage associated with this drug is only 10–50-fold, drug “A” would not be an attractive candidate for this method of delivery.

Conversely, if the cytotoxic potential of drug “B” is demonstrated to be highly concentration-dependent and the levels producing major tumor cell kill can only be achieved (at least in theory) at concentrations attainable following regional delivery (e.g., hepatic arterial infusion for colon cancer metastatic to the liver), drug “B” might be an ideal agent to consider for regional antineoplastic therapy.

3. THEORETICAL CONCERNS WITH REGIONAL ANTEOPLASTIC DRUG THERAPY

Despite the attraction of regional antineoplastic drug delivery in the management of cancers principally confined to a particular location in the body, there are a number of theoretical objections raised regarding this therapeutic concept.

First, even if one accepts the hypothesis that higher tumor–drug interactions (higher peak levels and AUC) associated with regional therapy will result in enhanced cytotoxicity, there is legitimate concern that the delivery of a drug to cancer cells not directly in contact with the perfused/infused area will not be beneficial. Furthermore, for regional treatments not employing the vascular compartment (e.g., intraperitoneal, intrapleural, intrathecal drug delivery), it might be argued that delivery of drug to tumor by capillary flow will be reduced, resulting in negative impact on therapeutic efficacy. Consideration of this issue leads to the conclusion that it is critically important to measure drug levels in the systemic compartment following regional delivery. If insufficient concentrations of drug are found in the systemic circulation following regional drug administration, it may be necessary to treat patients both regionally and intravenously to achieve optimal therapeutic results.

Second, it is well-recognized that despite the high concentrations achievable at the surface of tumor(s) following regional drug delivery, the actual depth of penetration of these agents directly into tumor tissue is quite limited (16–21).

Thus, the increase in tissue concentrations of drug following regional drug delivery, when compared to standard systemic treatment, is quite modest, despite the often extremely dramatic increases in drug concentration measurable in the plasma or the body cavity containing the tumor. This concern is particularly relevant for regional approaches not employing the vascular compartment, which rely exclusively on direct
uptake of drug from the body cavity for any therapeutic advantage associated with regional delivery.

This important issue leads to the logical conclusion that regional therapy will have its greatest theoretical potential for exhibiting an improved clinical outcome in patients with smaller tumor nodules or only microscopic disease in the perfused/infused body compartment. In these patients, the largest possible tumor volume will be exposed to the higher cytotoxic drug concentrations achievable with regional drug administration. Data generated evaluating the role of intraperitoneal therapy in the management of ovarian cancer strongly support this conclusion (22).

A third theoretical concern with regional delivery relates to unique considerations of the specific strategy in question. For example, it has been shown that when a drug is infused into a rapidly flowing blood vessel, the drug does not completely mix in the plasma (the so-called “streaming effect”), resulting in nonuniform drug distribution to the perfused tissue (23,24). The clinical impact of this laboratory observation is uncertain, but the potential exists that portions of the tumor within the organ will be exposed to significantly lower concentrations of drug than are necessary to achieve the desired optimal cytotoxic effect.

A second example is that of the potential for inadequate distribution of an antineoplastic agent instilled into a body cavity (e.g., peritoneum, pleura) (25–27). As blood flow through the region is not employed to deliver drug to the tumor, there is concern that regions of the body compartment will not be exposed to the necessary high concentrations of cytotoxic agent. This may be due to interference with uniform distribution by the presence of normal organs (e.g., bowel), tumor(s), or adhesions.

4. PRACTICAL CONSIDERATIONS ASSOCIATED WITH REGIONAL ANTINEOPLASTIC DRUG THERAPY

A number of practical issues must be considered when designing an experimental regional antineoplastic strategy or when employing a standard regional treatment approach in the clinical management of malignant disease (Table 4).

The establishment of safe, convenient, and cost-effective techniques for the administration of regional antineoplastic therapy is an important issue in the development of these strategies for routine clinical use.

For example, while a peritoneal dialysis catheter can be inserted at the time of each ip treatment, this method of delivery will significantly restrict the application of the regional approach. Only a limited number of physicians will feel comfortable with placing such catheters in patients who have previously undergone one or more laparotomies and who do not have ascites. In addition, time and resources required for this drug delivery technique can be considerable. Finally, even if employed by well-trained physicians, there is a finite risk that catheter insertion performed without direct visualization of the peritoneal cavity will lead to bowel puncture and associated complications (28,29).

The time, effort, and complications associated with achieving access to the arteries can pose greater concerns (30,31). For patients being considered for more than one or two courses of intraarterial therapy, the surgical placement of semipermanent delivery systems would appear to be the optimal method of regional drug delivery (31–33). This situation would also be relevant for patients scheduled to receive weekly or more fre-
quent intrathecal drug administration for the prevention or treatment of meningeal leukemia (34,35).

Considerable caution is advised regarding the potential for unique toxicities associated with regional antineoplastic drug administration. The toxicity profile of an antineoplastic agent may be well-established when the drug is administered systemically at standard dose levels. However, the side effects associated with the extremely high concentrations achievable following regional delivery, or the toxicity to tissues that would normally not come into direct contact with the drug after iv infusion, potentially may be excessive.

For example, the direct hepatic artery administration of FUDR can be associated with the development of sclerosing cholangitis or biliary cirrhosis (36,37); ip delivery of a number of cytotoxic agents, including doxorubicin or mitoxantrone, can lead to severe peritonitis, extensive adhesion formation, and subsequent bowel obstruction (8,38,39).

A number of proposed regional antineoplastic drug delivery methods require extensive surgery (e.g., isolation-perfusion of mesenteric arterial vessels, hyperthermic intraperitoneal chemotherapy), or are associated with considerable risk for the development of serious morbidity or death (40–42). Such strategies will require extensive evaluation and favorable results achieved in well-designed randomized trials before they can leave their current realm of highly experimental treatment programs and be considered reasonable therapeutic regimens in standard clinical practice.

Even regional antineoplastic drug delivery programs which do not require such intensity of treatment or are not associated with excessive toxicity will require the performance of randomized trials to be certain that the theoretical advantages of these novel therapeutic strategies can be translated into clinical benefit for individuals with malignant disease.

5. CLINICAL EXAMPLES OF REGIONAL ANTINEOPLASTIC DRUG DELIVERY

5.1. Intrathecal Therapy for the Prevention and Treatment of Meningeal Leukemia

One of the most established regional antineoplastic drug delivery approaches is that employed to either prevent or treat established leukemia in the central nervous system (2,43–45). In certain specific clinical settings, the risk for the development of meningeal involvement with leukemia has been demonstrated to be substantially
reduced with prophylactic intrathecal or intraventricular treatment. Established meningeal leukemia (documented by cerebral spinal fluid cytology) can also be effectively treated in many patients with several established regional antineoplastic drug regimens.

5.2. Intraperitoneal Therapy in the Management of Ovarian Cancer

The ip administration of antineoplastic agents in the management of ovarian cancer has been extensively examined in Phase I toxicity and pharmacology studies and Phase II efficacy trials involving a number of drugs with demonstrated activity in ovarian cancer, for example, cisplatin, carboplatin, paclitaxel, and/or doxorubicin (8,22,46).

More recently, the therapeutic potential of this method of drug delivery has been examined in the randomized Phase III trial setting (47,48). In a study involving newly diagnosed patients with small-volume, residual advanced ovarian cancer following surgical cytoreduction, the ip administration of cisplatin (in combination with iv cyclophosphamide) resulted in an improvement in overall survival, when compared with a control regimen of iv cisplatin administered with iv cyclophosphamide (47).

A recently reported randomized trial comparing iv cisplatin and paclitaxel with a regimen of iv paclitaxel and ip cisplatin has reached similar conclusions (48). This trial, also involving newly diagnosed advanced ovarian cancer patients with small volume residual disease, demonstrated a statistically significant improvement in progression-free survival and borderline improvement in overall survival associated with the regional treatment program. It should be noted that this study employed two courses of moderately dose-intensive iv carboplatin (AUC 9) prior to the administration of the regional program, designed to chemically debulk any residual tumor before the use of the regional drug delivery strategy.

5.3. Intrahepatic Arterial Therapy for Colon Cancer Metastatic to the Liver

Phase III trials have demonstrated a higher objective response rate associated with the direct intrahepatic arterial administration of FUDR, when compared to systemic delivery of the agent in the treatment of colon cancer metastatic to the liver (49–55). Several of these studies have been criticized because a crossover design was employed, whereby the patients randomized to iv drug delivery were permitted to receive intraarterial therapy at the time of disease progression. The impact of such crossover on the ultimate outcome has been debated extensively in the medical literature.

There have also been questions raised regarding the overall benefits of this strategy, in view of the morbidity and costs of the regional treatment approach. However, data available though the conduct of these trials support the clinical utility of this therapeutic strategy in carefully selected individuals with colon cancer metastatic to the liver. These clinical characteristics include adequate patient performance status, absence of serious comorbid medical conditions that might increase potential morbidity of the treatment regimen, and the presence of metastatic disease localized in the liver only.

5.4. Intravesical Therapy of Localized Bladder Cancer

The intravesical administration of both cytotoxic (e.g., mitomycin, thiotepa, doxorubicin) and biological (e.g., bacille Calmette-Guérin [BCG]) agents has been demonstrated to be effective treatment of superficial bladder cancer and carcinoma in situ in the bladder (56,57).
The ease of administering high concentrations of antineoplastic drugs directly into the bladder, and the simplicity of measuring the effects of treatment through the performance of urinary cytology and/or bladder wall biopsy, makes the bladder an ideal organ to employ regional therapy.

Intravesical antineoplastic therapy has been shown to prevent the progression from superficial to invasive cancer and to reduce the requirement for more radical surgical interventions, including the performance of a cystectomy.

6. CONCLUSION

Over the past decade, the regional administration of antineoplastic drugs has evolved from a theoretical concept to a rational treatment strategy in a number of clinical settings.

The rather profound pharmacokinetic advantage associated with regional drug delivery is appealing, but a number of theoretical and practical issues limit patient populations where this therapeutic approach is a reasonable option in both clinical trials and standard oncologic practice.

Randomized controlled trials will be required to demonstrate if the potential for enhanced tumor cell kill associated with increased drug concentrations and more prolonged exposure can be translated into improved outcomes for patients with malignant disease.

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