CANCER CHEMOTHERAPY CHALLENGES FOR THE FUTURE Vol. 4

CANCER CHEMOTHERAPY: Challenges for the Future Volume 4

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Preface

The Fourth Nagoya International Symposium on Cancer Treatment was successfully held from October 11 to 13, 1988, attended by about 400 oncologists. The proceedings of this symposium form the basis of this volume.

The book is divided into three parts. The first section, "Arterial infusion chemotherapy," covers aspects of its principles, pharmacokinetics, and clinical trials. The value of using such regional chemotherapy compared to systemic chemotherapy in randomized trial was discussed. Disease-oriented strategies, including chemotherapy regimens and the efficacy in terms of response rate and survival were presented and considered.

The second section, "Chemotherapy—curable solid tumors," covers childhood solid tumors, testicular tumors, and ovarian cancer. Major advances have been made in the management of childhood solid tumors. These advances were documented and evaluated in terms of treatment regimens and cure rate. Testicular tumors represented another demonstration of how therapeutic advances can be effectively implemented through use of diagnostic innovations and cisplatin-based chemotherapy. Encouraging results were also presented in ovarian cancer through use of aggressive chemotherapy which produced long-term survivors.

The third section is "Development of new drugs and clinical drug development methodology." The clinical development of new drugs is accomplished through the methodology of clinical trials. Current guidelines for conducting phase I-III study were presented, with emphasis on efficacy end points of phase III such as objective response, disease-free survival, survival, and quality of life. Principal aspects of requirements of the US FDA for cancer drug approval were also presented.

The clinical evaluation of new drugs related to problems in research, patient care, and regulatory matters was also reported, and clinical and regulatory challenges, currently facing new cisplatin analogues such as carboplatin, and registration strategies utilized in Europe, Japan, and the USA were also discussed.

The series of Nagoya International Symposia on Cancer Treatment began in 1985. Although not meant to be comprehensive, the objective of the series is to upgrade concepts in therapeutic strategy and preclinical studies, and to introduce developments in the major classes of compounds, identify new directions, and provide some landmarks of current clinical progress. Not only should this volume provide a comprehensive treatise on the role of cancer chemotherapy, but it should also give a perspective on future developments. Our gratitude is extended to all those who participated in and supported this effort.

Kiyoji Kimura

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I. ARTERIAL INFUSION CHEMOTHERAPY: PHARMACOKINETICS

Pharmacokinetic rationale for intraarterial therapy

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INTRODUCTION

Since all anticancer drugs have narrow therapeutic windows, it is natural to search for ways to specifically direct the effects of these drugs to the tumor rather than sensitive normal tissues. Intraarterial therapy provides one such approach to drug targeting. The primary goal of intraarterial therapy is to improve efficacy by producing selective changes in concentrations: to increase the concentration of drug delivered to tumors without raising the concentration of drug which is delivered to host tissues. In some circumstances, the strategic approach is to decrease host tissue concentrations without lowering tumor levels.

Although there is some tendency to try any drug in any disease area, pharmacologic principles can be used to select the most promising drugs and infusion sites. From a practical viewpoint, careful calculations can save years of clinical effort. Ideally, pharmacologic principles can focus resources into high-probability areas. Pharmacokinetic analysis can provide a rationale for intraarterial delivery, but a final evaluation of the utility of intraarterial therapy also requires consideration of the steepness of the dose-response curve and the rigorous challenge of controlled clinical trials.

This paper will describe the theoretical basis for such decision-making and give a specific example.

INCREASED DELIVERY OF DRUG TO THE TUMOR

The ability of intraarterial delivery to increase drug levels at the tumor site will be considered first. This is a comparative evaluation, relative to drug delivery via the intravenous route. Thus, the increased delivery to the tumor can be defined:

$$R_{tumor} = C_{tumor}(i.a.)/C_{tumor}(i.v.) \qquad [1]$$

Equation [1] is a general definition of the pharmacokinetic advantage of intraarterial delivery which can be used to evaluate experimental results. The next step in this analysis is to use pharmacokinetic modeling to develop

formulas which can be used to calculate R_{tumor} for various intraarterial situations.

Figure 1 illustrates our conceptual approach to the modeling of intraarterial drug delivery. If there is no elimination of drug by the organ being perfused, then R_{tumor} can be readily calculated. For the same dose of drug given intraarterially and intravenously, R_{tumor} is the ratio of tumor concentrations:

$$R_{tumor} = \frac{C_{tumor}(i.a.)}{C_{tumor}(i.v.)} = 1 + \frac{CL_{TB}}{Q} \qquad [2]$$

CL_{TB} is total body clearance of the drug, which can be found in the literature or determined from intravenous doses. Q is blood flow in the infused artery. The ratio of CL_{TB} to Q is the sole determinant of drug delivery advantage.

At first, it is appealing to assume that the rate of drug transfer across capillaries is an important factor for selection of compounds for intraarterial testing. However, since the evaluation of the drug delivery advantage for the intraarterial route is relative to systemic delivery, both routes share the same ease or difficulty of transcapillary passage.

Although first-pass extraction of a drug can be a useful property for increasing the advantage of arterial delivery (see next section), there is no absolute requirement for any first-pass effect. If the same dose is delivered intravenously or intraarterially, then Equation [2] describes the ratio of tumor concentrations regardless of the presence or absence of a first-pass extraction.

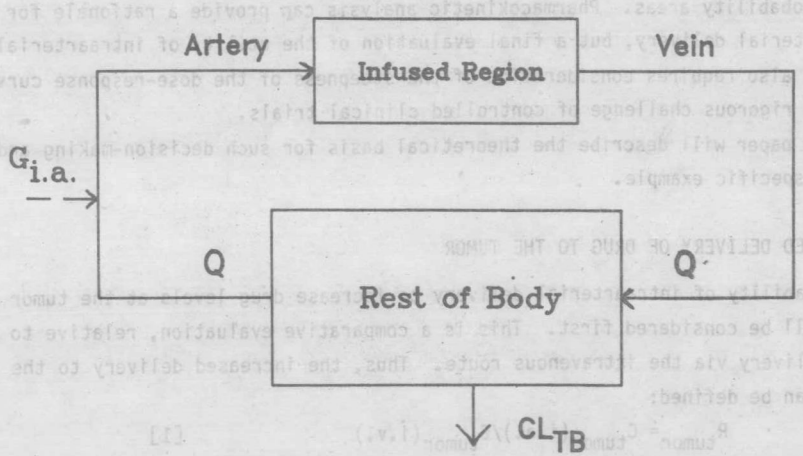

Figure 1. Schematic diagram for intraarterial infusion without a first-pass effect. Reprinted from Collins (1), with permission.

One of the conditions for Equation [2] is that the comparison between intraarterial and intravenous routes is based upon equal doses. This implies that the limiting host tissue is outside the site of direct infusion. If toxicity to local tissues is limiting, then intraarterial delivery of the same dose is not possible and the actual value for R_{tumor} will be lowered.

The drug delivery advantage can be calculated before doing an experiment or clinical study. Such calculations should influence the selection of drugs (based upon CL_{TB}) and infusion sites (based upon Q). As shown in Table 1, some drugs have such high CL_{TB} that they remain attractive regardless of the blood flow. Also, some drugs have such low CL_{TB} that they are not attractive candidates for any artery. However, the majority of agents fall in the middle area, so that a drug may be attractive in a low-flow situation, but not in a high-flow area.

TABLE 1

INTRAARTERIAL DRUG DELIVERY ADVANTAGE, R_{tumor}

Examples for selected anticancer drugs at high-flow (Q=1000 ml/min) or **low-flow** (Q=100 ml/min). Based upon Equation [2].

CL_{TB} ml/min	DRUG	R_{tumor} Q=100 ml/min	R_{tumor} Q=1000 ml/min
25000	Fluorodeoxyuridine	251	26
5000	Teroxirone	51	6
4000	Fluorouracil	41	5
3000	Cytosine Arabinoside	31	4
2500	Bromodeoxyuridine	26	3.5
1300	Iododeoxyuridine	14	2.3
1000	Carmustine	11	2
900	Doxorubicin	10	1.9
400	Diaziquone	5	1.4
400	Cisplatin	5	1.4
200	Methotrexate	3	1.2
40	Etoposide	1.4	1.04
--*	Cyclophosphamide	1	1

*Drugs which must be activated at a site other than the arterial infusion site have no drug delivery advantage.

FIRST-PASS EFFECTS: ELIMINATION OF DRUG BY THE PERFUSED ORGAN

If a certain fraction, E, of the infused dose is eliminated by the perfused organ (such as the liver), then 1-E is available to the systemic circulation. For equal doses:

$$R_{systemic} = \frac{C_{systemic}(i.a.)}{C_{systemic}(i.v.)} = 1 - E \qquad [3]$$

If acute systemic toxicity is dose-limiting, a larger dose can be given intraarterially than intravenously. If cumulative systemic toxicity is dose-limiting, then a larger number of doses (or a longer infusion) can be given intraarterially.

The overall pharmacokinetic advantage of intraarterial administration, R_d is composed of the increased local concentration and/or the decreased systemic concentration:

$$R_d = \frac{R_{tumor}}{R_{systemic}} = \frac{C_{tumor}(i.a.)/C_{tumor}(i.v.)}{C_{systemic}(i.a.)/C_{systemic}(i.v.)} \qquad [4]$$

If E=0, $R_{systemic}=1$ and $R_d = R_{tumor}$. When $E \neq 0$, $R_{systemic}$ is less than 1, which generally increases the overall value of R_d. However, in some cases, R_{tumor} is adversely lowered by local extraction. In fact, R_{tumor} can be reduced to 1 if the perfused organ is the sole site of drug elimination from the body.

The liver is frequently the principal organ of drug elimination. The anatomy of hepatic blood supply provides several options for intravascular drug delivery and for pre-systemic drug elimination. There can be differences for perfusion via the hepatic artery vs. the portal vein, particularly for large tumors (2). More specific details for the calculation of R_d for a variety of situations are presented elsewhere (3).

Some experimental studies have shown that the hepatic arterial route is superior to the portal venous route for delivery of drug to established (large) tumors. For small (micro) metastases in the liver, drug delivery via the portal route is probably as effective as via the hepatic artery.

MODIFIED APPROACHES TO INTRAARTERIAL DELIVERY

In order to maximize the drug delivery advantage, "superselective" catheterization is sometimes utilized, that is, the catheter is placed as close to the tumor site as possible. In pharmacokinetic terms (Equation [2]), this procedure increases the value of R_{tumor}, since the smaller the artery, the lower the blood flow.