3 Combination Chemotherapy by Infusion in Solid Tumors

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CONTENTS
3.1 Combinations Based on Infusional 5-Fluorouracil ........................................ 35
   3.1.1 Cisplatin and 5-Fluorouracil ...................................................... 36
   3.1.2 Mitomycin C/Infusional 5-FU Regimens ......................................... 41
   3.1.3 PALA/Infusional 5-FU Regimens .................................................. 41
3.2 Combination Chemotherapy Employing Infusional Bleomycin ........................................ 42
   3.2.1 Cisplatin/Infusional Bleomycin in Squamous Cell Lung Cancer ................. 42
   3.2.2 Cisplatin/Infusional Bleomycin in Non-Small Cell Lung Cancer ................ 42
3.3 Combinations Employing Infusional Etoposide ................................................. 43
3.4 Combinations Employing Infusional Vincas ................................................... 43
3.5 Conclusions and Direction of Continuing Research ........................................... 44
References ........................................................................................................... 44

Drug delivery by infusion is a promising avenue for improving the therapeutic index of several classes of drugs. Although the pharmacological rationale for infusional therapy has been long appreciated, relevant clinical trials have only recently begun to emerge, and only in a relatively few forms of cancer.

Infusional drug delivery can be used either to increase therapeutic efficacy or to reduce certain forms of toxicity; in some cases both objectives can be achieved simultaneously. Efficacy can be improved in the case of cycle specific drugs (e.g., antimetabolites) which have short plasma half-lives: increased exposure of cells during the sensitive part of the cell cycle increase killing. Another avenue for increasing efficacy is possible in synergistic combinations requiring increased duration of exposure. An example would be infusional schedules of a short-acting drug capable of inhibiting repair of alkylation damage of DNA, as has been suggested for bleomycin or etoposide. Some drug-related toxicities are related to peak drug levels rather than to area under the curve (AUC). If efficacy is related to AUC, equivalent doses delivered by infusion can reduce toxicity without sacrificing efficacy.

Thus, combination chemotherapy in which one or more drugs are given by infusion can be designed either based upon the infusional advantages of the drug by itself (in terms of efficacy or toxicity) or upon increased synergy resulting from the infusional schedule. This chapter will discuss such combination chemotherapy in the solid tumors.

3.1 Combinations Based on Infusional 5-Fluorouracil

The pharmacological and clinical advantages of infusional schedules over bolus schedules of 5-FU are irrefutably established. 5-FU, an S phase specific agent, has a plasma half-life of only 11 min (MACMILLAN et al. 1978). Yet solid tumors typically have only a small fraction of cells in S phase at any time. For example, thymidine pulse labeling studies in most human solid tumors show labeling indices of only 2%-10% (SHACKNEY 1985). Thus, a bolus dose of 5-FU reaches only a small fraction of cells during the susceptible period. Infusional schedules increase the fraction of cells exposed during S phase. Both long-term continuous infusion schedules and shorter-term (typically 5-day) infusions have been utilized for this purpose. A recent example of the striking advantage of infusional over bolus schedules of 5-FU comes from the Mid-Atlantic Oncology Program (MAOP) prospective randomized trial in 179 patients with metastatic colorectal cancer. In this study an aggressive bolus schedule of 5-FU (500mg/m² qd × 5 every 5 weeks) was compared with protracted continuous infusion 5-FU at 300 mg/m²/day. There was a fourfold increase in objective response rate (30% vs 7%, P < 0.001) favoring the infusional arm, and complete responses (5%) were seen only...
in the infusional arm (Lokich et al. 1989). The reduction in toxicity with the infusional schedule was equally impressive. Whereas there was a 13% incidence of serious (grade 3) and a 7% incidence of life-threatening (grade 4) hematological toxicity with the bolus schedule (and four drug-related neutropenic deaths), only one patient on the infusional schedule experienced any degree of myelosuppression, and there was no grade 4 toxicity of any cause on the infusion arm.

Regimens in which one or more additional drugs are combined with infusional 5-FU have been investigated in a number of malignancies. The most frequently investigated drugs have been cisplatin and mitomycin C, but methotrexate, bleomycin, and others have also been studied.

### 3.1.1 Cisplatin and 5-Fluorouracil

Preclinical studies have shown a high degree of synergy between cisplatin and 5-FU in sensitive cell lines. Even on a single-dose schedule marked synergy was noted in L1210-implanted mice (Dionet and Verrelle 1984; Schabel et al. 1979). These results have led to the use of cisplatin with infusional 5-FU in a variety of tumors, and an impressive clinical benefit has been observed in some.

#### 3.1.1.1 Cisplatin/Infusional 5-FU in Squamous Carcinoma of the Head and Neck

Little attention has been given to protracted infusion schedules of 5-FU in head and neck cancer, but shorter infusion schedules, typically 5 days at doses of the order of 1 g/m²/day given in combination with cisplatin, have been widely investigated. This combination yields response rates of the order of 80%–90% when given as initial therapy (Table 3.1), with complete response rates in the range 20%–50%, and probably represents the most widely used chemotherapy regimen in head and neck cancer today. When administered to patients with recurrent disease after radiotherapy or chemotherapy, a wider range of response rates, 10%–70%, has been reported (Table 3.2). Even in recurrent disease some complete responses, up to 20% in some series, are reported.

Because of the high response rate of head and neck cancer to cisplatin/infusional 5-FU, it has been speculated that induction chemotherapy with this regimen may improve survival and/or cure rate when it is given prior to surgery or radiotherapy. However, to date, no randomized trial has yet demonstrated such an advantage. Randomized trials in the past using other less active chemotherapy regimens have been consistently negative (Tannock and Brown 1986). Trials are underway to test cisplatin/infusional 5-FU as induction therapy in a prospective randomized setting. One comparison of three successive pilot studies suggests that superior induction chemotherapy may influence survival irrespective of subsequent radiotherapy or surgery (Rooney et al. 1985).

Cisplatin/infusional 5-FU has also been studied in combination with simultaneous radiotherapy, both preoperatively and as definitive treatment in head and neck cancer. Taylor, Murthy, and co-workers (Murthy et al. 1987; Taylor et al. 1985, 1988a) combined cisplatin (60 mg/m²), 5-FU (800 mg/m²/day × 5), and radiotherapy (2 Gy × 5) in cycles repeated every 2 weeks. Seven cycles were given to 50 patients, with a lesser number of cycles given palliatively to patients with distant

### Table 3.1. Trials of cisplatin/infusional 5-FU in previously untreated squamous carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Cisplatin dose</th>
<th>5-FU dose</th>
<th>Frequency</th>
<th>CR + PR</th>
<th>CR</th>
<th>Patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/m²</td>
<td>1000 mg/m²/day × 5</td>
<td>q 3 wk</td>
<td>93%</td>
<td>54%</td>
<td>61a</td>
<td>Rooney et al. 1985</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>1000 mg/m²/day × 4</td>
<td>q 3 wk</td>
<td>88%</td>
<td>19%</td>
<td>26b</td>
<td>Rooney et al. 1985</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>1000 mg/m²/day × 4</td>
<td>q 3 wk</td>
<td>88%</td>
<td>19%</td>
<td>26b</td>
<td>Kish et al. 1982</td>
</tr>
<tr>
<td>80 mg/m²</td>
<td>800 mg/m²/day × 5</td>
<td>q 3 wk</td>
<td>84%</td>
<td>23%</td>
<td>31</td>
<td>Amsterdam and Weitzman 1985</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>1000 mg/m²/day × 5</td>
<td>q 3 wk</td>
<td>83%</td>
<td>33%</td>
<td>30c</td>
<td>Jacobs et al. 1987</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>1000 mg/m²/day × 5</td>
<td>q 4 wk</td>
<td>84%</td>
<td>26%</td>
<td>19d</td>
<td>Dasmahapatra et al. 1985</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>1000 mg/m²/day × 5</td>
<td>q 3 wk</td>
<td>87%</td>
<td>37%</td>
<td>70e</td>
<td>Kies et al. 1985</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>1000 mg/m²/day × 5</td>
<td>q 3 wk</td>
<td>77%</td>
<td>17%</td>
<td>23f</td>
<td>Haas et al. 1985</td>
</tr>
</tbody>
</table>

a Response rate evaluated after three cycles of therapy  
b Response rate evaluated after two cycles of therapy  
c Six patients received bleomycin rather than 5-FU