Protracted drug infusions in cancer treatment: An appraisal of 5-fluorouracil, doxorubicin, and platinums

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Summary
The feasibility to deliver chemotherapeutic agents by protracted i.v. infusion has greatly increased in the recent past. Indwelling ports, longer lasting central venous catheters requiring less than daily maintenance 'flushing', surgical expertise in placement, use in analgesia and nutrition, and 'smart' pump technology have all contributed to their increasing popularity. Justification for use of infusions in cancer chemotherapy has been slow in appearing with few studies proceeding to the comparative stage. This review will focus on three drugs in common use in cancer treatment, with the purpose of appraising the role of such infusions in cancer therapeutics and of deriving some lessons that might be applicable to other drugs or to drug development in general. For fluorouracil and doxorubicin the rationale and clinical findings favoring further development of infusion regimens is particularly strong. In the case of platinum compounds, some toxicologic advantages have emerged, but other measures designed to protect against the toxicities of cisplatin compete with infusion regimens in this regard. The therapeutic potential for this form of drug delivery, therefore, appears still confined to a subset of patients. Stronger rationales for the use of protracted infusions may be forthcoming from pharmacodynamic findings as in the case of etoposide, combined modality therapy with radiation for FU and cisplatin, biochemical modulation for FU, and reversal of multidrug resistance and its modulation for doxorubicin. While awaiting research into these areas of clinical and pre-clinical investigations, the role of infusion appears most evident in the cardio-toxicity protection of anthracyclines, and in further efficacy exploration (through dose or modulation) of FU. Both mechanistic and pharmacologic considerations could also provide additional stimulus for development of new formulations such as long circulating liposomes, and drugs more suitable for oral administration.

Key words: cisplatin, continuous infusion, doxorubicin, 5-fluorouracil, infusion, protracted infusion

Introduction
Several reviews have appeared on the use of protracted infusion of cancer chemotherapeutic agents [1–5], and a quarterly Journal of Infusional Chemotherapy was introduced in 1991 which was to include in each issue 'a series of four to five articles on the state-of-the-art on a topic related to infusional chemotherapy'. This review will focus on three drugs in common use in cancer treatment, with the purpose of appraising the role of such infusions in cancer therapeutics and of deriving some lessons that might be applicable to other drugs or to drug development in general. The drugs were selected because of the role such infusions currently play in cancer treatment. Before dealing with the individual drugs it is worth reflecting why other drugs are not similarly utilized.

Alkylating agents appear to have little schedule dependency in experimental tumor systems, and do not yield obviously different results clinically by altering schedules. The oxazaphosphorines in high doses to require an infusion for their administration, but there is no evidence of improved antitumor effect by prolonging the infusion [6–8]. The vinca alkaloids have enjoyed a brief popularity by more prolonged infusion, but endothelial toxicity and lack of convincing improvement in therapeutic index have led to a decline in popularity of infusions [9]. Dacarbazine has been given in 4 day infusions for sarcomas, but this agent has a limited role and an unconvincing alteration in toxicity spectrum by this schedule [10–12]. The rationale for prolonged exposure to etoposide concentrations that may be cytotoxic to tumor cells but have less myelosuppressive potential has been a noteworthy development of the past few years. These studies have been carried out primarily with an oral formulation [13, 14]. Finally, methotrexate, a markedly schedule dependent drug has been given in infusions varying from 6 to 24 hours in order to standardize high dose regimens with rescue [15], and a similar rationale has been advanced for cytarabine [16, 17]. In neither instance have protracted infusions been widely adopted. Taxol has, of course, been introduced into widespread clinical use as a 24 h infusion and shows strikingly less myelosuppression when given over 3 h. However, as we shall describe under doxorubicin, there is interest in more prolonged infusions as a possible means to overcome drug resistance [18, 19].
5-fluorouracil (5-FU, FU)

Mechanistic considerations

**Sensitivity.** The debate on whether FU exerts its antitumor effects via inhibition of thymidylate synthetase (TS), or via incorporation into RNA, or both has spanned two decades. The clear demonstration that increasing folate cofactor pools altered the clinical efficacy and toxicity spectrum of FU was held as confirmatory of the central role of TS inhibition and stabilization of 5-fluorodeoxyuridylate (FdUMP) with the enzyme in a ternary complex when excess 5,10-methylene tetrahydrofolate is present [20]. However, Martin [21] has argued persuasively that experimental conditions demonstrating enhancement of FU effects by folates utilized sub optimal doses of FU; it is at high doses that RNA mechanisms of cytotoxicity come into play [22]. Scheduling is key in biochemical modulation: prolonged exposure to FU in vitro shows marked enhancement in cytotoxicity with the introduction of leucovorin, whereas this enhancement falls exponentially with shorter exposure times [23]. Clinically, mucositis is seen frequently with protracted infusion FU schedules when modulated with low (20 mg/m²) weekly doses of leucovorin, suggesting that this finding is operative in this clinical toxicity [24]. What is totally unknown is whether some clinical toxicities and antitumor effects represent DNA inhibition or the contribution of RNA mechanisms.

**Resistance.** The dual mechanism of action of FU may be a factor in preventing the emergence of resistance. Recently, Bertino and colleagues have characterized differences in resistance features of cells in vitro when exposed repeatedly for brief periods to FU, or following prolonged exposure to subtoxic doses. Resistance following prolonged exposure was related to a failure to retain folate cofactors (i.e., defective folylpolyglutamyl synthetase), whereas resistance to brief exposures was related to defective activation of the pyrimidine base [25]. This finding does encourage a crossover of schedules upon treatment failure.

Pharmacological considerations

The short half life of FU by i.v. push, and the variable capacity of individuals to catabolize it, lead to considerable spread in concentration × time (C × T area under curve, AUC) patterns [26, 27]. It is likely that in the absence of demonstrable toxicity many patients receive inadequate doses of FU. This fact alone probably explains repeated observations of activity when previously treated patients are again exposed to more intensive FU regimens, with or without modulation. Sub optimal dose-schedules of FU are most prominent when the drug is given in fixed combinations such as CMF for breast cancer. Infusion schedules of FU generally achieved greater AUCs than the intermittent schedules [26, 27]. Moreover, the pharmacology of infusion schedules has been better characterized in terms of its pharmacodynamic effects on toxicity and efficacy. In two studies [28–30] it was clearly shown that FU AUCs correlated with toxicity, with only a trend demonstrated for efficacy. A major advantage of protracted infusion schedules is that one may more regularly arrive at a reproducible level of toxicity, than with i.v. push FU. Another advantage could relate to the ability to achieve biochemical modulation with low doses of folates; this advantage, however, needs to be demonstrated in clinical studies. Some have also argued that cytokinetic considerations favor protracted infusion [31]. However, one must recall the experiment of Young et al. on recovery of DNA synthesis in gut and L1210 cells as a reminder that the intracellular events outlast by days any pharmacologic measurements [32].

Given the premise that infusions constitute an important way to optimize the dose of FU being delivered, questions arise with regards to the actual dose and duration of infusions. Weekly 24 h infusions have been given at a dose of 2600 mg/m² [33]. Generally in combination with other drugs such as cisplatin or mitoxantrone, infusions ranging from 72 h (1000 mg/m²/d) and up to 5 days have been given [51, 54, 56, 61]. In more protracted infusions, the usual dose often given in combination with radiation because of its lack of myelosuppression is of 300 mg/m²/d until mild stomatitis or other toxicities; the MTD exceeded 500 mg/m²/d for 28 d in a phase I study of FU alone [34]. Although FU is not suitable for oral administration, the pro drug Ftorafur has been combined with the competitive inhibitor of catabolism of FU, uracil, in a 1:4 molar ratio. This combination marketed in Japan as UFT (Taiho) has proven to be a reliable way to achieve therapeutic levels of FU. It is usually administered on a split dose 2 to 3 times per day indefinitely or until toxicity which supervenes after an average of 2 to 4 weeks depending on the dose. Its toxicity spectrum differs somewhat from infusion in producing more diarrhea and less stomatitis [35].

FU shows remarkable circadian regulation in pharmacokinetics in both rodents [36, 37] and humans [38]. Diasio has shown that this variation may be caused by diurnal changes in the activity of dihydropyrimidine dehydrogenase, a catabolic enzyme whose activity in human leukocytes nadirs at 6 p.m. and peaks in the early morning [38, 39]. Variation in bone marrow S phase is less prominent but it also shows periodicity with a peak at noon [144, 145]. Circadian modified schedules have been used for treatment of colon cancer with FU and oxaliplatin [40], and for treatment of renal cell cancer with fluorodeoxyuridine [41]. Although pharmacologically sound, and model based, such schedules have not been compared in rigorous trials with schedules generally used. Therefore, they will not be considered further in this review, while stressing the need for future study.
Clinical results

Toxicity. Continuous infusion FU exhibits a different pattern of dose-limiting toxicity when compared to i.v. push FU. Whereas weekly i.v. push results in dose-limiting myelosuppression and erratic gastrointestinal toxicity, the daily × 5 i.v. push (at 450 mg/m²/d results primarily in diarrhea within 1–2 weeks of completion, and less frequently delayed myelosuppression. Both of these effects are less frequent when the drug is given by protracted infusion. The dose limiting toxicity of such infusion is mucositis followed by diarrhea. The use of continuous infusion has also resulted in the appearance of a new toxicity, palmar-plantar erythrodysesthesia (hand-foot syndrome) [42, 43]. This syndrome occurs with accelerated frequency when leucovorin is given, perhaps indicative of a relation to prolonged DNA inhibition. Recovery is seen after a few days interruption, and built in intervals with no treatment have proven helpful in limiting its severity [24].

Chest pains with electrocardiographic changes have also been more common with infusion that i.v. push administration of FU. These appear to be true ischemic syndromes in many instances [44, 45], and a relation to an impurity in European preparations has also been hypothesized. On the other hand, some chest pains with radiation to the neck and occasionally to either arm, we believe are related to vasalgia in relation to the infusion. This pain occurs most often when there is proximal venous occlusion, but may occur in the absence of an occlusion, and improves with non-steroidal analgesics or by stopping the infusion. Occasionally we have seen this pain with drugs other than FU, such as ifosfamide of vinca alkaloids, but most often the culprit has been FU, perhaps because of more ubiquitous use.

Efficacy. Seifert et al. first reported a trial comparing 120 h infusion FU compared to the standard i.v. push regimen for treatment of colorectal cancer. The results showed a 42% response for the continuous infusion arm, which was twice that of the other arm; survival was not affected [46]. Subsequent studies reviewed by Vogelzang also failed to demonstrate improved survival [1]. The Middle Atlantic Oncology Group (MAOP) study reported by Lokich indicated a better therapeutic index for the continuous 14-day infusion with a markedly better response rate (7% for the daily × 5 i.v. push versus 30% for the infusion) [47]. More recent studies by Rougier [48] and by the Southwest Oncology Group show only trends favoring continuous infusion, but no major differences in response rates or survival of advanced colorectal cancer [49, 50]. A recent report by Leichman indicates a 56% response rate in a single institution pilot of a 28-day infusion with weekly leucovorin [24], but again group studies show only trend favoring infusions and modulation, but no significant differences relative to conventional FU dose-schedules.

Protracted FU infusion is an attractive alternative in metastatic breast cancer that has undergone much prior treatment, because of its minimal myelosuppression, its excellent subjective tolerance, the usual sub optimal prior exposure to FU, and the frequent requirement for central venous catheters during late stages of disease. Table 1 indicates reported studies of continuous infusion for the treatment of metastatic breast cancer. More recently interest has shifted to earlier stages of disease, with several studies being performed in combination with other drugs [51–59]. Combinations with radiation may also hold some interest in locally advanced breast cancer.

In head and neck cancer, cisplatin and 4-day infusions of FU have been commonly used. Kish et al. reported in 1985 on a prospective trial comparing continuous infusion of FU for 5 days to a weekly bolus FU. A substantial response rate in favor of the infusion arm was noted (72% vs. 20%) [62]. More protracted infusions in combination with radiation have been adopted for the treatment of cervical cancers [63] and esophageal cancers in combination with cisplatin as well [64].

Doxorubicin (adriamycin, Dx)

Mechanistic considerations

Sensitivity. Dx may have more than one mechanism of tumor cytotoxicity including topoisomerase II mediated.

Table 1. Regimens utilizing infusional 5-fluorouracil in the treatment of breast cancer.

<table>
<thead>
<tr>
<th>Study/institution</th>
<th>n</th>
<th>dose</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palangie, 1986 [51]</td>
<td>34</td>
<td>FU 500 mg/m²/d CI × 5d (+CTX IVB, +VDS IVB)</td>
<td>50%</td>
</tr>
<tr>
<td>Jabboury, 1988 [52]</td>
<td>27</td>
<td>FU 250 mg/m²/d PTI × 3–5 week</td>
<td>26%</td>
</tr>
<tr>
<td>Hansen, 1987 [53]</td>
<td>25</td>
<td>FU 200–300 mg/m²/d PTI × 5d &gt;5 weeks</td>
<td></td>
</tr>
<tr>
<td>Fracchini, 1987 [54]</td>
<td>5</td>
<td>FU 500 mg/m²/d CI × 5d (+VLB)</td>
<td>32%</td>
</tr>
<tr>
<td>Strauss, 1988 [55]</td>
<td>11</td>
<td>FU 300 mg/m²/d PTI + (+CDDP 20 mg/m²/week)</td>
<td>27%</td>
</tr>
<tr>
<td>Wallach, 1989 [56]</td>
<td>18</td>
<td>FU 300 mg/m²/d PTI × 14d (+CTX 100 mg/m²/d PTI × 14d +MTX 0.75 mg/m²/d PTI × 14d)</td>
<td>65%</td>
</tr>
<tr>
<td>Huan, 1989 [57]</td>
<td>28</td>
<td>FU 175–250 mg/m²/d PTI to toxicity</td>
<td>53%</td>
</tr>
<tr>
<td>Hartfield, 1989 [58]</td>
<td>69</td>
<td>FU 300 mg/m²/d PTI</td>
<td>18%</td>
</tr>
<tr>
<td>Chang, 1989 [58]</td>
<td>10</td>
<td>FU 200–300 mg/m²/d PTI to toxicity</td>
<td></td>
</tr>
<tr>
<td>Gordon, 1990 [59]</td>
<td>37</td>
<td>FU 250 mg/m²/d PTI (DXR 15 mg/m² IVB weekly cxt 60 mg/m²/d PO daily)</td>
<td>83%</td>
</tr>
<tr>
<td>Lokich, 1993 [60]</td>
<td>33</td>
<td>FU 300 mg/m²/d × 10 w PTI + 2 w rest</td>
<td>14%</td>
</tr>
<tr>
<td>Jones, 1991 [61]</td>
<td>53</td>
<td>FU 1000 mg/m²/d × 3d CI LV 100 mg/m²/d × 3d IVB MTZ 10–12 mg/m² IVB q 21 d</td>
<td>45%</td>
</tr>
<tr>
<td>Iveson 1993 [143]</td>
<td>41</td>
<td>FU 200 mg/m²/d PTI × 6m CDDP 60 mg/m² i.v. q 3w</td>
<td>75% (MD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPi 50 mg/m² IVB q 3w</td>
<td>92% (LA)</td>
</tr>
</tbody>
</table>

Abbreviations: PO = by mouth, i.v. = intravenous, IVB = intravenous bolus, CI = continuous intravenous infusion, PTI = protracted intravenous infusion, FU = 5-fluorouracil, CTX = cyclophosphamide, MTX = methotrexate, LV = leucovorin, DXR = doxorubicin, MTZ = mitoxantrone, VLB = vinblastine, VDS = vindesine, CDDP = cisplatin, EPI = epirubicin, MD = metastatic disease, LA = locally advanced, d = day, w = week, m = month
ed DNA double and single strand breaks, DNA intercalation, generation of free radicals, cell membrane effects including decrease fluidity, and inhibition of DNA-pol-alpha and RNA-polymerase. It is unclear which mechanism is operative at clinically achievable concentrations of Dx. It does seem likely that cardiac damage is mediated by inadequate defenses in cardiac tissue against activated oxygen species leading to generation of free radicals and lipid peroxidation [65]. These free radicals may arise via formation of a Dx-iron complex [66], and protection against cardiac toxicity has been noted with the precursor of an intracellular chelating agent, ICRF-187 or desrazoxane (ADR-529). Antitumor effects are retained in the presence of ICRF-187 in murine systems, but additional clinical experience is required to be certain that no abrogation occurs in the efficacy of Dx. The initial trial in breast cancer comparing Dx + ICRF-187 versus Dx, both as part of combinations with cyclophosphamide and FU yielded equivalent response rates and survival with clear protection against cardiac events [67]. On the other hand, clear protection against cardiac toxicity is achieved by infusion regimens, with 6 h infusions conferring no protection, and increasing cumulative doses of Dx being possible as one proceeds from 24 h through 48 and 96 h infusions, to the protracted infusion exceeding 14 days, where cardiac toxicity is not observed or is very slowly cumulative [68–73].

Resistance. Mutations in topoisomerase II [74, 75], and overexpression of p-glycoprotein (Pgp) encoded by the multidrug resistance gene (mdr) are the two commonly recognized causes of resistance to Dx [76]. Both may be operative in some experimental cell systems. Extreme (greater than 20 fold) levels of resistance may be noted, and in the case of overexpression of Pgp is associated with a decrease in intracellular levels of Dx. As early as 1973, Dano recognized this was due to excessive efflux of Dx, and than this efflux could be decreased by simultaneous exposure to a non-cytotoxic chelating agent, ICRF-187 or desrazoxane (ADR-529). Correlations between intracellular Dx levels and cytotoxicity do not always hold up, and some have argued that changes in the cell membrane triggered subsequent nuclear events may be key in explaining cytotoxicity, and lack of this 'trigger' occurring by signal transduction is the cause of Dx resistance [78]. Pumps other than Pgp may be implicated in resistance of some tumors such as lung cancer [79].

Pharmacological considerations

Anthracyclines show little schedule dependency in experimental murine systems. Nevertheless, both experimental and clinical evidence support the exploration of dose-schedule alterations to increase efficacy, decrease toxicity, or overcome resistance. Analogues have also been introduced to improve on the therapeutic index of Dx. These will not be discussed further, although one advantage of epirubicin may be its biphasic pharmacokinetics avoiding the long terminal half life of Dx which could give rise to less predictable drug-radiation interactions and more prolonged toxic effects [80]. Liposomal Dx preparations may provide an alternative for prolonged infusions, as improved preparations are entering clinical study [81–83]. Liposomal Dx has also been shown to retain some activity against Pgp-mediated resistance [84].

The importance of a protracted Dx exposure on cytotoxicity in vitro is supported by some experimental observations against Sarcoma 180 grown in plateau phase by Ritch et al. [85]. Prolonged exposure times were more effective than brief exposures to high concentrations. Eicholtz-Wirth has shown that the cytotoxicity of Dx to Chinese Hamster and HeLa cells was proportional to the product of the extracellular drug concentration (c) and exposure time (t) according the equation SF = e^{-kt} where SF indicates the survival fraction and k is a constant indicating sensitivity of the cells [86]. In tumor-bearing animals, Storm et al. [87] utilizing the Lou/M Wsl rat tumor showed reduction in cardiotoxicity by Dx by infusion or encapsulated Dx, but not by shorter (24 h) infusions, or by bolus. The antidotal effect was equivalent. Reversal of Dx resistance with verapamil was shown by Slate and Michelson [88] to increase the survival of (C57BL/6×DBA/2) (BDF1) animals bearing P388/ADR when treated with both continuous infusion (3 mg/kg/d × 7 d) or intermittent (10.5 mg/kg IP × 2) schedules. Dx alone by either schedule showed little efficacy in this resistant model.

Animal studies support better tolerance of schedules mimicking infusion. We have already mentioned lessening cardiac toxicity in the tumor-bearing rat model. In dogs, Garnick et al. showed the toxic dose low of Dx to be 0.2 mg/kg/d i.v. push, and 0.1 mg/kg/d by continuous infusion. These doses are equivalent to 2 mg/m²/d and have been subsequently used in clinical studies with protracted infusion [72]. The pharmacokinetics of prolonged Dx infusion in man have been well delineated. Clearance mechanisms in dose ranges from 0.2–6.1 mg/m²/d are not saturated for 2 to 50 weeks [89–91]. Similar findings were observed with prolonged infusions of 1–5 mg/m²/d for 14 days [72]. In analogous studies at the University of Chicago the maximum steady state concentration was 6.04 ng/ml at a mean maximum infusion rate at 3.92 mg/m²/d. Clearance mechanisms were not saturated. Some variation in metabolite or parent drug urinary excretion was noted by Sweatman et al. comparing short term (5d at 10–15 mg/m²/d) to longer term infusions (50–104d at 3 mg/ m²/d); ratios of Dx to doxorubicinol were not consistent, and aglycones were only occasionally present [92].

Clinical results

Toxicity. Attenuation of cardiotoxicity through infusions longer than 24 h has been convincingly demonstrated in several studies, principally with 96 h infu-
tions in protocols at MD Anderson [69, 71]. More pro-
longed infusions appear to have strikingly reduced
cardiotoxic potential, including our own experience with a
patient receiving doses exceeding 1500 mg/m² over 17
months (Wang and Muggia, unpublished) and had no
drop in ejection fraction. The same patient did manifest
the unusual toxicity more typically associated with FU
infusions, palmar-plantar erythrodysesthesia; in addi-
tion she experienced loss of finger- and toe-nails, and
nodular lung changes in an area which had been pre-
viously exposed to radiation given postoperatively fol-
lowing her mastectomy. Other experience with infusion
does report the skin changes [93]. On the other hand,
protracted infusions are generally well tolerated by the
patient with virtual elimination of nausea and vomiting
when at a dose of 3 mg/m²/day (Table 2). A potential
danger, however, with subcutaneously implanted ports,
is that of extravasation leading to the very problematic
dermal necrosis. At present there is insufficient experi-
ence to comment on toxicity of infusion protocols in-
cluding resistance modifiers such as verapamil. One
study with 96 h infusion demonstrated the feasibility of
combining Dx with high doses of verapamil, but an
intensive care level of monitoring was required [94].

Other than potentiation of arrhythmogenic and cardio-
toxic potential, there could be concern about enhanced
hepatobiliary and even CNS toxicities that are being
examined in current phase I trials combining Dx in a
48 h infusion with cyclosporin [95].

**Efficacy**

Comparison between infusion and i.v. push regimens
have taken place only to a limited extent and confined
to 96 h infusions (Table 3). Randomized studies in
non-small cell lung cancer were primarily carried out
for a cardiotoxicity endpoint [96]. Response and sur-
vival were the endpoints of a Southwest Oncology
Group study in advanced soft tissue sarcomas. No dif-
ferences have been noted, except in the toxicity spec-
trum noted above [97]. In advanced breast cancer
where Dx has a major role, only a randomized phase II
study versus infusion FU has been carried out [98].
Activity has been noted in this trial as well as in some
of the phase I trials of protracted infusion [99]. With
our understanding of mechanisms of resistance, the
rationale has been advanced that infusions may be able
to overcome Pgp-mediated efflux, and hence, resis-
tance. Pre-clinical studies cited above suggest resistance
modifiers may still be needed. Nevertheless, such a
strategy is more easily conceived employing infusion
schedules than i.v. push administration.

### Table 2. Protracted infusion doxorubicin (> 120 hr) ambulatory regimens in the treatment of solid malignancies.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dose</th>
<th>Total</th>
<th>Durat</th>
<th>Toxicity</th>
<th>RR</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garnick, 1983</td>
<td>14</td>
<td>2.5-4</td>
<td>956</td>
<td>22 w</td>
<td>H, S, A, N-V</td>
<td>1/14</td>
<td>Phase I</td>
</tr>
<tr>
<td>Lokich, 1983</td>
<td>56</td>
<td>2-5</td>
<td>&gt;450</td>
<td>180 d</td>
<td>H, S, A</td>
<td>5/52</td>
<td>Several</td>
</tr>
<tr>
<td>Speth, 1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samuels, 1987</td>
<td>17</td>
<td>3-5.5</td>
<td>1097</td>
<td>212 d</td>
<td>H, S, A, h-f</td>
<td>3/17</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Hartfield, 1989</td>
<td>18</td>
<td>2.5-3</td>
<td>-</td>
<td>-</td>
<td>H, S, A</td>
<td>0/18</td>
<td>Breast</td>
</tr>
<tr>
<td>Ackland, 1989</td>
<td>32</td>
<td>0.2-0.6</td>
<td>-</td>
<td>50 w</td>
<td>S, H, A</td>
<td></td>
<td>Sarcoma, Breast, Kidney, Prostate</td>
</tr>
<tr>
<td>Sweetman, 1989</td>
<td>8</td>
<td>3</td>
<td>104 d</td>
<td>H, S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jasmin, 1990</td>
<td>27</td>
<td>2.2-4.5</td>
<td>1647</td>
<td>&gt;60 d</td>
<td>H, S, A</td>
<td>4/24</td>
<td>Breast</td>
</tr>
</tbody>
</table>

* a mg/m²/day; *b mg/m²; *c d = days, w = weeks; *d H = hematologic, S = stomatitis, A = alopecia, h-f = hand-foot syndrome, N-V = nausea or vomiting.

### Table 3. Infusional doxorubicin regimens utilizing doxorubicin as a 48 to 96 h infusion i.v.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dose</th>
<th>Schedule</th>
<th>RR</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legha, 1982</td>
<td>27</td>
<td>60</td>
<td>CI 96-hr</td>
<td>13/27</td>
<td>Breast</td>
</tr>
<tr>
<td>Hortobagyi, 1989</td>
<td>133</td>
<td>60</td>
<td>IVB</td>
<td>81%</td>
<td>Breast</td>
</tr>
<tr>
<td>Ackland, 1989</td>
<td>79</td>
<td>60</td>
<td>CI-48 hr</td>
<td>80%</td>
<td>Breast</td>
</tr>
<tr>
<td>Ackland, 1989</td>
<td>62</td>
<td>60</td>
<td>CI-96 hr</td>
<td>76%</td>
<td>Breast</td>
</tr>
<tr>
<td>Zalupski, 1991</td>
<td>118</td>
<td>60</td>
<td>IVB</td>
<td>17%</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Casper, 1991</td>
<td>122</td>
<td>60</td>
<td>CI-96 hr</td>
<td>17%</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Lokieh, 1992</td>
<td>67</td>
<td>60</td>
<td>IVB q 3w</td>
<td>25%</td>
<td>Breast Ca</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>60</td>
<td>IVB q1 w</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>60</td>
<td>CI 96 h q3 w</td>
<td>44%</td>
<td></td>
</tr>
</tbody>
</table>

* a mg/m² per cycle; *b d = days, 2 = weeks, m = months
PO = by mouth, i.v. = intravenous, IVB = intravenous bolus, CI = continuous intravenous infusion, PTI = protracted intravenous infusion.
Platinum compounds

Mechanistic considerations

Cisplatin and other organoplatinums do not show schedule dependent activity against experimental tumors in mice [100]. Nevertheless, in vitro and cytokinetenic considerations are often provided as rationale for exploring infusion regimens of platinum [101–105]. More importantly, the ability to overcome cisplatin's renal toxicity is facilitated by infusion, and this allows greater dose intensity of cisplatin to be administered safely [106, 107]. Jacobs et al. have demonstrated that interference with tubular secretion of cisplatin through probenecid administration allows safe dose-escalation of cisplatin on a 24 h infusion schedule [108]. Emesis is also reduced by the infusion schedule. The increase in dose per cycle that is possible does not, however, exceed 50% because other toxicities, such as neurotoxicity, become apparent. Thus, advantages by the use of infusion schedules are likely to be minor. Finally, combinations with radiation or other drugs (Table 4) may provide some rationale for infusion: in one instance by providing constant exposure which may result in greater radiosensitization [109, 110] and in another instance to take advantage of circadian rhythms in optimizing dose intensity [11, 112]. The analogue oxaliplatin has been used alternating with FU in a circadian-based 5-day infusion schedule in patients with colorectal cancer [113]. A preceding phase I study had demonstrated better tolerance of circadian-based schedule in preventing neurotoxicity, than a constant infusion schedule [114]. Infusion has also been the preferred way of delivering high doses of carboplatin in marrow ablative regimens prior to autologous bone marrow transplantation [115].

Pharmacological considerations

Some comparative pharmacokinetic data exists for cisplatin when given by i.v. push versus infusion schedules. The studies generally indicate 10 to 40 times lower peak levels of ultrafilterable platinum, but greater AUCs with 5 day infusion schedules [116–120]. Serial study indicates some increase in AUC with repeated administration, corresponding to diminished renal excretion [119]. Gandara et al. in comparing 40 mg/m²/d x 5 (infused over 30 minutes in hypertonic saline) versus 100 mg/m² d 1 and 8 (given in a similar way) also showed some accumulation in ultrafilterable platinum with repeated daily doses [121]. As noted earlier, during infusion schedules one may effectively block cisplatin tubular secretion with probenecid, while reabsorption is not saturated [108]. With large i.v. push doses of cisplatin, reabsorption capacity is saturated, perhaps explaining differences in AUC.

Clinical results

Toxicity. Dose-schedule alterations as well as hydration were extensively studied during the first decade of cisplatin use. Salem and colleagues first called to the attention of clinicians the change in toxicity spectrum by utilizing 5 day infusions [123]. On this schedule emesis was considerably attenuated, and leukopenia was more frequently observed. Subsequent experience with this schedule suggested it also resulted in a greater propensity to develop peripheral neuropathy. With the advent of better anti-emetic regimens and the introduction of carboplatin, this rationale for the infusion schedule weakened considerable. It should be noted, however, that the troublesome ototoxicity of cisplatin is not well protected against with increasing dose, and that it seems to bear some relationship to peak platinum levels. Therefore, exploration of infusion cisplatin schedules under some circumstances seems warranted. If our ability to protect against neurotoxicity improves, infusion schedules may hold the key for further safe dose escalation together with toxicity protectors.

Efficacy. Comparative trials have focused on toxicity issues, and little difference in efficacy is to be expected except what might be achievable by increasing the dose-intensity of cisplatin. As already mentioned, the increase in dose-intensity is, however, quite modest. Moreover, few regimens can exceed the dose intensity of 50 mg/m²/w that can be given for periods of up to 6–8 weeks. Nevertheless, a number of pilot studies have been done in patients with head and neck and non-small cell lung cancers (Table 5). The studies show encouraging results, but at present do not provide sufficient rationale for embarking in comparative trials.

Table 4. Role of drug scheduling in continuous infusions: In vitro effects of CDDP (P) simulating continuous infusion (C) or short infusions for 1 hour (1) in several sequences and schedules in combination with VP16 (V), bleomycin (B) and mitomycin-C (M) using clinically achievable concentrations, against HEC-1A endometrial carcinoma cells and 8226 myeloma cells. Modified from reference 151.

<table>
<thead>
<tr>
<th>Drugs and sequence</th>
<th>Effects in</th>
<th>HEC-1A</th>
<th>8226</th>
</tr>
</thead>
<tbody>
<tr>
<td>V + P (C)</td>
<td>antagonistic</td>
<td>synergistic</td>
<td>additive</td>
</tr>
<tr>
<td>V (1), P (C)</td>
<td>synergistic</td>
<td></td>
<td>additive to antagonistic</td>
</tr>
<tr>
<td>M + P (C)</td>
<td>antagonistic</td>
<td>synergistic</td>
<td></td>
</tr>
<tr>
<td>M (1), P (C)</td>
<td>antagonistic</td>
<td>synergistic</td>
<td></td>
</tr>
<tr>
<td>B + P (C)</td>
<td>antagonistic</td>
<td>synergistic</td>
<td></td>
</tr>
<tr>
<td>B (1), P (C)</td>
<td>antagonistic</td>
<td>synergistic</td>
<td></td>
</tr>
<tr>
<td>B + M + P (C)</td>
<td>synergistic</td>
<td></td>
<td>additive</td>
</tr>
<tr>
<td>B (1), M (1), P (C)</td>
<td>antagonistic</td>
<td>synergistic</td>
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</tr>
<tr>
<td>M (1), B (1), P (C)</td>
<td>additive</td>
<td></td>
<td>additive</td>
</tr>
<tr>
<td>B + V + P (C)</td>
<td>additive</td>
<td></td>
<td>synergistic</td>
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<tr>
<td>B (1), V (1), P (C)</td>
<td>additive</td>
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<tr>
<td>V (1), B (1), P (C)</td>
<td>synergistic</td>
<td></td>
<td>synergistic</td>
</tr>
</tbody>
</table>

* 1 — exposure to drug for 1 hr; c = continuous exposure; + = simultaneous use of drugs; , — sequence as written.

b Using individual drug IC75.
Conclusions

The feasibility to deliver chemotherapeutic agents by protracted i.v. infusion has greatly increased in the recent past. Indwelling ports, longer lasting central venous catheters requiring less than daily maintenance 'flushing', surgical expertise in placement, use in analgesia and nutrition, and 'smart' pump technology have all contributed to their increasing popularity. Justification for use of infusions in cancer chemotherapy has been slow in appearing with few studies proceeding to the comparative stage. For fluorouracil and doxorubicin the rationale and clinical findings favoring further development of infusion regimens is particularly strong. In the case of platinum compounds, some toxicologic advantages have emerged, but other measures designed to protect against the toxicities of cisplatin compete with infusion regimens in this regard. The therapeutic potential for this form of drug delivery, therefore, appears still confined to a subset of patients.

Stronger rationales for the use of protracted infusions may be forthcoming from pharmacodynamic findings as in the case of etoposide, combined modality therapy with radiation for FU and cisplatin, biochemical modulation for FU, and reversal of multidrug resistance and its modulation for doxorubicin. While awaiting research into these areas of clinical and pre-clinical investigations, the role of infusion appears most evident in the cardiotoxicity protection of anthracyclines, and in further efficacy exploration (through dose or modulation) of FU.

On the negative side, infusions while attenuating some toxicities, increase the likelihood of morbidity related to infections or endothelial damage. In addition, they often require procedures for central catheter placement, and demand a certain adjustment in lifestyle. Nevertheless, throughout this review we have stressed findings that provide the logic for pursuing this approach in the future. Both mechanistic and pharmacologic considerations could also provide additional stimulus for development of new formulations such as long circulating liposomes, and drugs more suitable for oral administration.

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