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Review

Dose intensity for bolus *versus* infusion chemotherapy administration: Review of the literature for 27 anti-neoplastic agents

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Summary

Problem: The dose intensity (DI) and the maximum tolerated dose (MTD) of anti-neoplastic agents is assumed to be a critical factor for achieving optimal therapeutic benefit. Each of these factors may be influenced by the schedule of drug administration, specifically infusional or bolus delivery.

Objective: To review the literature for selected antineoplastic drugs to analyze the relative DI and MTD for bolus vs. infusional administration schedules.

Methods: Clinical reports of bolus and infusional delivery of chemotherapeutic drugs in the categories of antimetabolites; alkylating agents; antibiotics; plant alkaloids and platinum analogues were collected focusing on phase I studies establishing the MTD per cycle and the DI. Infusional schedules were defined as continuous parenteral administration for more than 24 hours or, in some instances, daily bolus dosing for one hour for 3 to 5 days. Bolus schedules were defined as administration over minutes up to 24 hours and also included daily dosing in some cases.

Results: For antimetabolites, the infusional schedule generally decreases the MTD and DI relative to bolus administration but for 5-FU, the MTD and DI both increase. For alkylating agents and the platinum analogues, the MTD and DI for bolus and infusional delivery are generally comparable; but infusional administration results in a slightly increased MTD for thiotepa and for ifosfamide, the MTD is increased depending upon the duration of the infusion. For the antibiotics and the plant alkaloids, the MTD and DI of infusional administration is variable related to the specific agent and the infusion duration and may be increased, decreased or comparable to the MTD of bolus schedules.

Conclusions: The MTD and DI for most cytotoxic agents administered by bolus *versus* infusional schedules is unpredictable and variable and is influenced by the infusion duration and the interval between treatment cycles (for example three *versus* four week intervals). The MTD and DI increase substantially with infusional delivery for thiotepa, 5-FU and VM26 (the latter in leukemia specifically) and decrease substantially for the antimetabolites FUDR, ara-C, methotrexate and 6MP. For most other agents and in all four drug categories, the MTD and DI are relatively comparable although for ifosfamide and topotecan, the duration of infusion determines whether the MTD and DI increases, decreases or stays the same relative to bolus administration. The use of cytokines may substantially change the MTD and DI especially for bolus administration since dose limiting toxicity is hematologic for many agents.

Key words: bolus chemotherapy, dose intensity, infusion

Introduction

Some anti-neoplastic agents are administered as a continuous 24-hour infusion for five or more days routinely, such as 5-fluorouracil and cladrabine. Some agents, for example, fludarabine and etoposide are administered as a daily bolus for three to five days emulating an infusional schedule and may be considered as a type of infusion in spite of bolus administration because of the constancy of delivery. The rationale for infusional administration for chemotherapeutic agents is generally based upon observing schedule dependency in experimental systems and drug pharmacology in which a short plasma half-life following bolus administration would limit tumor cell exposure (Table 1) [1]. Furthermore, the infusion schedule may mitigate the acute and chronic toxicities commonly associated with high peak levels.

Infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96–120-hour infusions; 7- or 14-day infusions; and finally the protracted infusion for weeks or months. The selection of a duration of infusion is often arbitrary or based on achieving specific objectives such as decreasing allergic, gastrointestinal or other adverse effects. The dose intensity (DI) and the maximum tolerated dose (MTD) for infusional schedules may be different from those achieved with bolus administration and as such may influence the clinical effectiveness of the therapy.

We undertook to review the literature with regard to the phase I and/or phase II studies for selected antineoplastic agents in order to compare the MTD and DI of bolus and infusional administration. We define bolus administration as a less than 24-hour administration period and infusional administration as a 24-hour or more continuous administration. Phase I and/or phase II studies of single agent administration without the planned use of cytokines were part of the criteria for

Table 1. Pharmacologic half of selected antineoplastic agents.

Drug class	T½ (hours)
Anti-metabolites	
5-Fluorouracil	0.16
Methotrexate	2–4
Fludarabine	10
Ara-C	1
2 CD A	4–20
Hydroxyurea	3
6Mercaptopurine	0.83 (Gamma)
Alkylating agents and platinums	
Cyclophosphamide	4–6.5
Ifosfamide	15
Melphalan	2
Mitomycin C	0.75
Thiotepa	1.6
Carboplatin	1.3–1.7 (Beta)
Cisplatin	1 (Beta)
Antibiotics	
Doxorubicin	3.3
Epirubicin	18
Mitoxantrone	23–42
Actinomycin	36
Bleomycin	2–4 (Beta)
Plant alkaloids	
Paclitaxel	5.8 (Beta)
Etoposide	6–8 (Terminal)
Teniposide	8 (Terminal)
Topotecan	2.6 (Mean)
Vincristine	23-85 (Gamma)
Vinblastine	20–64 (Gamma)
Vinorelbine	18–49 (Gamma)
Vindesine	20–24 (Gamma)

Modified from Vogelzang, J Clin Oncol 1984; 2: 1289 [1].
Supplemented and updated from Chabner BA and Longo DL, Cancer Chemotherapy and Biotherapy, 2nd Edition 1995, Lippencott-Raven Philadelphia, New York.

selection of the drugs to be studied. Twenty-seven agents were identified for review within four categories, including antimetabolites, alkylating agents, antitumor antibiotics and plant alkaloids.

Antimetabolites

Antimetabolites as a group are cycle specific agents and schedule dependent for the most part in experimental systems and in clinical usage. Some of the agents are provided in an oral formulation and routinely are administered on a schedule emulating parenteral infusion, for example 6mercaptopurine and hydroxyurea. Five of the agents (ara-C, hydroxyurea, 6MP, fludarabine and cladribine) have been employed almost exclusively in the treatment of hematologic malignancies with dose limiting toxicity manifest as bone marrow suppression but the therapeutic goal within the context of treating these malignancies is also marrow suppression. For hydroxyurea and cladaribine, no bolus dosing studies have been reported (Table 2).

5-Fluorouracil (5-FU)

The fluoropyrimidines (5-FU and 5-FUDR) represent classic, if not quintessential, anti-metabolites commonly administered utilizing an infusion schedule. For 5-FU, short-term infusions for 24 or 48 hours on a weekly basis as well as 5-day, 7-day, 14-day and protracted infusion schedules have been reported [2–6]. The most common bolus schedule is daily × 5 repeated at 5-week intervals with an MTD of 500 mg/m^2/d or 2500 mg/m^2/cycle. Dose limiting toxicity (DLT) is leukopenia. For infusional 5-FU, the MTD for a 5-day infusion is 5 g/m^2 and for the protracted infusion for 28 days 8.4 g/m^2 [7]. The protracted infusion dose limiting toxicity was established in a phase I trial in which the DLT was manifest as hand-foot syndrome in 25% to 30% of patients in those receiving the infusion at a rate of 300 mg/m^2/day for more than 30 days. For this fluoropyrimidine, therefore, the infusional schedule results in a substantial increase in the dose intensity by a factor of 4 and the dose limiting toxicity is substantially changed from bone marrow suppression to stomatitis or hand-foot syndrome most probably related to differences in pharmacologic distribution of the drug, sparing the bone marrow.

Floxuridine (5-FUDR)

Floxuridine is most commonly applied in the setting of hepatic arterial infusion. Studies of systemic bolus *versus* infusional administration for five days revealed a marked decrease in the MTD with infusional delivery [8]. Protracted infusions of 5-FUDR for 14 days demonstrated that the MTD was only 0.15 mg/kg/day which translated to a cumulative dose of 777 mg/m^2 for a cycle [9]. In contrast to 5-FU, the dose intensity for infusional delivery of 5-FUDR decreases by a factor of greater than 7 relative to bolus administration but dose limiting toxicity is similar to that on the bolus schedule.

Cytosine arabinoside

This agent is virtually never employed in a bolus schedule and even the high dose ara-C bolus regimens utilize an every 12 hours delivery for six or more doses emulating an infusion. Nonetheless, a phase I trial by Frei et al. demonstrated a substantial decrease in the MTD for ara-C administered on the infusional schedule compared to bolus delivery [10]. Dose limiting toxicity is non hematologic since bone marrow suppression is the expected therapeutic effect and is manifest as neurologic toxicity particularly cerebellar dysfunction but hepatic toxicity and dermatologic toxicity can also be observed. Dose intensity is decreased by a factor of 10 or more in the transition from the high dose 'bolus' regimens to the 7-day infusional regimen but the comparison is complicated by the fact that the bolus schedule is tantamount to infusional administration and a case may be made for the high dose regimen simply being a special type of infusion.

Table 2. Antimetabolites: Comparison of maximum tolerated dose (MTD) per treatment cycle and dose intensity (DI) for bolus *versus* infusion administration.

Agent	Bolus		Infusion		Reference
	MTD mg/m^2	DI mg/m^2/wk	MTD mg/m^2	DI mg/m^2/wk	
5-FU[a]	2000–2500	500–525	5000[1] 8400[2]	1250 2100	2–6
5-FUdR[b]	5500	1387.5	777	194.2	8, 9
Ara-C[c]	36000	9000	2800	700	10
Hydroxyurea (HU)[d]	ND	ND	10000	3333	11–13
6Mercaptopurine[e]	2400	800	210-350	52.5–87.5	14–17
Fludarabine	160	40	110 to 125	27.5–31	18, 19
Cladribine	107.5	28	49	12	20
Methotrexate[f]	200	200	21	5.25	21

[a] Weekly bolus (500 mg/m^2) or daily × 5 (525 mg/m^2) *versus* 5 day infusion[1] or protracted 28-day infusion[2] (2.1 g).
[b] Mg/kg transposed to mg/m^2 using multiple factor of 37.
[c] Bolus 3 g/m^2 over 3 hours q 12 h × 12 doses *versus* infusion × 7 days at 200 to 400 mg/m^2/d.
[d] Infusion for 120 hours; No data for parenteral bolus.
[e] Bolus = 24-hour infusion in AML or 48-hour infusion in solid tumors.
[f] Infusion for 28 days. Bolus without leucovorin rescue.
Abbreviation: ND – no data.

Hydroxyurea (HU)

A direct comparison of bolus and infusional administration of hydroxyurea has not been reported in part because the parenteral formulation has not yet been approved by the FDA but also because bolus administration is not a common usage. Early studies of short term infusion by Belt et al. [11] and Blumenreich et al. [12] of 72-hour or longer duration infusions have been reported and Doroshow [13] has completed a phase I study of 120-hour infusional HU with dose limiting toxicity manifest as bone marrow suppression. For the 72-hour schedule, the MTD was 324 g/m^2 (oral) or 778 g/m^2 (intravenous) with DLT manifest as leukopenia. For the Blumenreich study, the study objective was to determine the maximum duration of infusion at different doses and at 500 mg/m^2/day HU could be administered indefinitely similar to the experience with protracted 5-FU infusion. However, according to Doroshow, for the 5-day infusion the maximum cumulative dose was 12.5 g/m^2 with DLT of skin rash and neutropenia and the DI, which may require cytokine support, is 3.25 g/m^2/week. Therefore, prolonging the infusion from 72 to 120 hours apparently results in a substantial decrease in MTD but low daily dose rates can permit extension of the infusion duration.

6Mercaptopurine (6MP)

Like hydroxyurea, 6MP has been employed predominantly in hematologic malignancies, with an oral formulation mimicking infusion, and the FDA has not yet approved the use of the parenteral form of the drug. Nonetheless, short term infusion studies have been reported, although for relatively short periods less than 48 hours [14, 15], and for longer periods in solid tumors in relatively older trials [16]. Thus, the bolus doses defined in Table 2 for 6MP actually represent 24- or 48-hour infusions and the data for more protracted infusions are limited to one study in which 6MP was administered for up to 10 days in an experimental design that provides inconclusive data. In the latter study, patients received up to 35 mg/m^2/d for 6 to 10 days by continuous infusion. A minor proportion of patients achieved DLT with leukopenia and it may well be that substantially higher doses are achievable. These data suggest that the infusion schedule decreases the MTD and DI for 6MP but a more modern and sophisticated phase I trial for infusion is necessary. Such a phase I study with a classical experimental design is ongoing utilizing the parenteral formulation with a 14-day infusion duration. A preliminary analysis indicates that the MTD for a 14-day infusion is 420 mg/m^2 with a dose intensity of 105 mg/m^2/week [17]. The dose limiting toxicity is neutropenia and hyperbilirubinemia.

Fludarabine

Fludarabine is a schedule dependent antimetabolite in experimental systems and is employed as a therapy for low grade lymphomas with the dose limiting toxicity and therapeutic effect being bone marrow suppression. Phase I trials have utilized a 48-hour infusion schedule [18] or a daily × five schedule emulating an infusion [19]. The total cumulative dose per cycle of approximately 125 mg/m^2 for the daily × 5 bolus can be compared to 110 mg/m^2 for the loading dose – 2-day infusion schedule and the single bolus dose schedule which is 160 mg/m^2. The MTD for the three schedules increases as the duration of administration decreases from five to three to one day.

Cladribine (2CDA)

2-Chlorodeoxyadenosine is an antipurine which is administered as a continuous infusion for seven days as

Table 3. Alkylating agents and platinum analogues: Comparison of MTD per treatment cycle and DI for bolus *versus* infusional administration.

Agent	Bolus		Infusion		Reference
	MTD mg/m^2	DI mg/m^2/wk	MTD mg/m^2	DI mg/m^2/wk	
Cyclophosphamide[a]	2000	666	2000	666	22–25
Ifosfamide	7500	1875	7000[2]	1750	26–29
			18000[3]	4500	
Thiotepa[b]	14	4.1	60[1]	15	30
			112[2]	28	
Cisplatin[c]	100	25	100	25	31
	200	50			
Carboplatin[d]	400–600	80–120	375[1]	75	32–34
			350[2]	70	

[a] Infusion 120 hours or 28 days.
[b] Infusion 120 hours or 28 days.
[c] Infusion 5 days.
[d] Use of dosing formula based on creatinine clearance and the delayed asymetric leukopenia-thrombocytopenia complicate the DI calculation for both bolus and infusional administration.
[1] 5-Day infusion.
[2] 14-Day infusion.
[3] 4-Day infusion.

a standard schedule based upon experimental *in vitro* studies which demonstrate schedule dependency and a pharmacology profile with a short plasma half-life of only 6.7 hours. Bolus schedules have been explored using a daily × 5 schedule [20]. Dose limiting toxicity for the infusion schedule is bone marrow suppression which is also the intended therapeutic effect but neurologic effects are observed as well. In contrast, daily bolus dosing obviates or minimizes the neurologic effects. The MTD for a 7-day infusion is 49 mg/m^2 compared to 107.5 mg/m^2 for the 5-day bolus schedule.

Methotrexate

The antifolate compound methotrexate represents an antimetabolite which is most commonly employed in breast cancer as part of the CMF regimen at a dose of 40 to 60 mg/m^2 parenteral bolus twice monthly or in the context of lymphomas or head and neck cancer tumors utilizing 'intermediate' or high dose regimens weekly. The MTD indicated in Table 2 for the bolus schedule represents the 'intermediate' high dose methotrexate regimen which may be administered without the need for leucovorin rescue and can be delivered on a weekly basis. Dose limiting toxicity is stomatitis. For the infusion regimen, a phase I trial of protracted 14-day infusion of methotrexate resulted in dose limiting toxicity of stomatitis and thrombocytopenia [21]. The dose intensity is reduced by a factor of almost 40 on the infusion schedule compared to the bolus schedule or even higher if the high methotrexate doses administered with leucovorin rescue are considered.

Alkylating agents and platinums

The alkylating agents are a diverse group of compounds only three of which are parenterally formulated and stable enough to be administered as an infusion (cyclophosphamide, ifosfamide and thiotepa) (Table 3). Melphalan is stable for only three hours and is therefore not practical for ambulatory infusion and the nitrosoureas are also unstable with the exception of streptozocin. There are also oral formulations of some of the alkylating agents (melphalan, chlorambucil, cyclophosphamide) which are often utilized in a schedule which emulates parenteral infusional delivery. The two major platinum analogues, cisplatin and carboplatin, are considered non classical alkylating agents and although both have been administered on an infusional schedule, the current rationale for infusional administration based upon pharmacology or an improved therapeutic index has not been established for either of these agents. In fact, although some experimental data suggests that for some alkylating agents an infusional schedule may be advantageous, there is no clinical data supporting an advantage for an infusional schedule and there have been no randomized comparative trials of infusional *versus* bolus administration of single agents. Dose limiting toxicity for all the alkylating agents as well as carboplatin is bone marrow suppression and for cisplatin is neurologic and renal complications.

Cyclophosphamide

Infusional cyclophosphamide has been studied in 72-hour [22], 120-hour [23, 24] and protracted infusion for 14 days or more [25]. The maximum tolerated dose for all of these durations of infusion was approximately 2000 mg/m^2 with dose limiting toxicity manifest as leukopenia with minimal thrombocytopenia. In the two studies addressing the five day infusion, one was carried out in refractory leukemia and one in solid tumors the latter focusing on pharmacology studies. The study in solid tumors demonstrated that the area under the curve (AUC) for phospheramide mustard is three times higher with the infu-

sional administration of cyclophosphamide compared to bolus dosing. Another pharmacodynamic aspect of this agent is the requirement for microsomal activation which may obscure possible differences between infusion and bolus administration.

It is evident from these studies that for cyclophosphamide the dose intensity is comparable whether one uses an infusional delivery or bolus administration.

Ifosfamide

The analogue of cyclophosphamide is most commonly administered as a daily bolus or as a continuous infusion over five days. In order to obviate the problem of hemorrhagic cystitis with bolus dosing, a common administration schedule is as a fractionated bolus daily for five days with concomitant Mesna administration. In a phase I study of 4-day continuous infusion ifosfamide along with Mesna uroprotection, dose escalation to a maximum dose of 18 g/m^2 was possible and dose limiting toxicity was renal insufficiency and central nervous system toxicity [26]. For 10-day infusion periods, the maximum cumulative dose decreased to 12 to 13 g/m^2 [27] and in a phase I trial of protracted infusion of ifosfamide for 14 days, the MTD was 7 g/m^2 per cycle [28]. Therefore, the MTD and DI for infusional ifosfamide may be increased or decreased relative to bolus delivery depending on the duration of infusion. Although phase III trials of infusional *versus* bolus ifosfamide have not been carried out, one study did analyze a sequential group of patients receiving ifosfamide as a bolus and subsequent entries as an infusion in conjunction with a combination chemotherapy regimen for metastatic sarcoma and there was a higher response rate in the group receiving bolus ifosfamide [29].

Thiotepa

The alkylating agent thiotepa is uncommonly used but has been employed as an alkylating agent in the treatment of Hodgkin's disease replacing nitrogen mustard because of the absence of gastrointestinal toxicity and it has also been used as part of a combination chemotherapy regimen for breast cancer. Dose limiting toxicity for bolus administration is bone marrow suppression as it is for infusional delivery. Only a single phase I trial has been carried out for thiotepa using a continuous infusion schedule. The cumulative dose for a 5-day infusion is 60 mg/m^2 and for the more protracted infusion of 28 days, the cumulative dose is almost doubled to 112 mg/m^2 [30]. Therefore, for this particular alkylating agent, the MTD and dose intensity is increased by a factor of 4 to 7 on the infusion schedule compared to the bolus schedule.

Platinum analogues

The two major platinum analogues are cisplatin and carboplatin, each of which demonstrate a different dose limiting toxicity and toxicity which is generally not altered with the use of the infusional schedule. For cisplatin, the continuous infusion schedule was introduced as a potential option for decreasing extra-medullary toxicity such as renal, neurologic toxicity and gastrointestinal toxicity [31]. However, the same pattern and frequency of toxicities are observed on the infusional schedule as the bolus schedule and the doses achieved per cycle are similar with a comparable dose intensity.

For carboplatin, the dose limiting toxicity is bone marrow suppression with markedly reduced gastrointestinal and renal toxicity compared to cisplatin. Bolus dosing is commonly guided by the Calvert formula and the MTD for bolus scheduling varies between 400 and 600 mg/m^2 and could be higher. The infusional schedule has been explored in a phase I study with a decrease in the cumulative dose per cycle and a modest decrease in the dose intensity [32]. Other studies of continuous infusion carboplatin have suggested that the dose intensity may in fact be increased. For example, in the study by Smit et al. [33], the cumulative dose for a 21-day infusion was 630 mg/m^2. However, because of the delayed pattern of hematologic toxicity associated with carboplatin, this infusional schedule could only be administered at 6-week intervals. Thus, the dose intensity is calculated to be approximately 105 mg/m^2 which is comparable or slightly less than that achieved with bolus administration depending upon the Calvert formula calculation.

The trials of continuous infusion carboplatin in refractory leukemia utilized a cumulative dose of 1500 mg/m^2 per cycle [34]. Although demonstrating activity in acute leukemia, the precise calculation of the dose intensity for carboplatin is complicated by the pattern of delayed and protracted myelosuppression. Nonetheless, assuming an interval of up to 6 or 7 weeks between cycles of treatment, the potential dose intensity nearly doubles to 200 mg/m^2 per week with infusional delivery compared to bolus administration at least in the trials involving carboplatin for leukemia.

Antibiotics and anthracenediones

A comprehensive review of infusion administration of antineoplastic antibiotics has been previously published [35]. The antibiotic agents that have been studied using an infusion schedule include the anthracycline analogues doxorubicin and epirubicin and the, anthracendione, mitoxantrone and three unrelated antibiotics mitomycin C, actimycin D and bleomycin (Table 4).

Doxorubicin was the earliest anthracycline to be introduced and is the most commonly employed agent in this category in the United States while epirubicin is popular in Europe. The acute dose limiting toxicity is bone marrow suppression and stomatitis and the cumulative dose for both analogues is limited by cardiac effects and particularly cardiomyopathy. Short term and protracted infusion schedules were actually developed in order to obviate the problem of cumulative cardiac toxicity and dose rate limiting toxicity for both the acute and chronic

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