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Choice of starting dose and escalation for phase I studies of antitumor agents*

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Summary. The standard approaches to initial dose selection and dose escalation in phase I trials may be inappropriately conservative. These approaches mandate accrual of large numbers of patients, most of whom are treated at low and potentially ineffective doses. We compared the clinically determined maximum tolerable dose (MTD) with the starting dose of 45 drugs that had undergone phase I studies during the period 1977–1989. We also examined the number of dose-escalation steps required to achieve the MTD in relation to nonhematologic and hematologic dose-limiting toxicity. The median ratio of MTD to starting dose for all drugs was 20 (range, <1–433) and the median number of dose levels studied to reach the MTD was 8 (range, 0–23). For drugs with nonhematologic dose-limiting toxicity, the median ratio of MTD to starting dose was 30 (range, 3–385) as compared with 12.8 (range, <1–433) for those with hematologic dose-limiting toxicity ($P = 0.023$). The median number of dose-escalation steps required to reach the MTD was 9 (range, 2–18) for drugs with nonhematologic dose-limiting toxicity as compared with 5.5 (range, 0–23) for those with hematologic dose-limiting toxicity ($P = 0.038$). We also examined the response rate for 1,110 patients treated with 21 phase-I-study drugs for which response information was available. Responses were reported for 29 patients (2.6%). Among the 476 patients treated at the 3 highest dose steps, 17 responded (3.6%), which is double the response rate obtained at the lower doses ($P = 0.08$). It is suggested that although the usual methods for choosing starting doses and dose-escalation schemes for phase I studies are safe, they are overly conservative and delay opportunities for therapeutic benefit in phase I and subsequent phase II trials.

Introduction

The primary objectives of phase I studies of antitumor agents are to determine the maximum tolerated dose (MTD) for a given schedule and route of administration and to estimate the qualitative and quantitative toxicity profile. Secondary objectives include the identification of antitumor activity and the estimation of pharmacokinetic and pharmacodynamic parameters. Early in the history of the development process for phase I trials, preclinical toxicology studies were used to define the toxic dose low (TDL) in dogs and monkeys for safety considerations in clinical trials; one-third of the TDL in the more sensitive species was chosen as a safe starting dose for phase I trials of antitumor agents [10]. Later studies suggested that the mouse could serve as a model for predicting quantitative toxicity in humans [5]. Further results suggested that one-third of the lethal dose (LD_{10}) in mice would be a safe starting dose and would decrease the number of dose-escalation steps required to reach the MTD as compared with one-third of the TDL in dogs and monkeys [9]. One-tenth of the mouse LD_{10} has been found to be a safe starting dose as long as that dose is not lethal or life-threatening to dogs. This provides the commonly used basis for initial doses in phase I studies [11]. The usual approach for escalating doses above the starting dose, the modified Fibonacci search scheme, was initially applied to phase I studies on nitrosourea and epipodophyllotoxin drugs [7, 8].

The present report compares the clinically determined MTD with the starting dose of 45 antitumor agents, examines the number of dose-escalation steps required to achieve the MTD according to nonhematologic or hematologic dose-limiting toxicity, and examines the relationship between the frequency of response and the level of dose escalation for patients entered into phase I studies.

Patients and methods

A total of 45 drugs that had undergone phase I study between 1977 and 1989 in the United States and Europe were reviewed. These drugs were

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Table 1. Median ratio of MTD to starting dose and median number of dose-escalation steps required to reach the MTD

Number of drugs	Median ratio of MTD to starting dose (range)	Median number of dose-escalation steps (range)
45	20 (<1–433)	8 (0–23)
25[a]	30 (3–385)	9 (2–18)
18[b]	12.8 (<1–433)	5.5 (0–23)

[a] Nonhematologic dose-limiting toxicity
[b] Hematologic dose-limiting toxicity

chosen because data were available for their starting doses, MTDs, and dose-limiting toxicities. They also represent a wide variety of chemical structures and mechanisms of action. The starting dose for most drugs was one-third of the TDL in dogs or some fraction of the mouse LD_{10} usually one-tenth. The starting dose for carbetimer was $^1/_{20}$ of the LD_{10}, and that for didemnin B and echinomycin was $^1/_{30}$ of the LD_{10}. The starting dose for Ara-AC was $^1/_{50}$ of the nontoxic dose in mice. The Fibonacci search scheme was usually followed for dose escalation. When the method of dose escalation was not specified, the Fibonacci search scheme was assumed. There was no standard definition for the MTD. Authors did not usually specify which toxicity grade had to be experienced by how many patients at a given dose level; rather, the MTD was usually the highest escalated dose that did not produce life-threatening toxicity for a given schedule.

Response data for 1,110 patients treated at each dose-escalation step were available for 21 drugs. The overall response rate was calculated first for patients treated at all dose levels and then separately for those treated at the highest dose examined or within two steps of the highest dose.

The Wilcoxon test was used to compare drugs that produced hematologic dose-limiting toxicity with those that caused nonhematologic dose-limiting toxicity. Drugs associated with both kinds of dose-limiting toxicity were omitted from the comparison. If a drug was studied on more than one schedule, we applied only the smallest ratio of MTD to starting dose (and the smallest number of dose-escalation steps), although the analysis was repeated using the largest of these values. To ensure that the results would be conservative, we reported *P*-values derived from the comparison using the smallest ratio of MTD to starting dose (and the smallest number of dose-escalation steps), since these were higher (that is, less statistically significant). All *P*-values are two-sided. In computations of median values and ranges, all schedules were used. A chi-square test was used to compare the response rates for the higher versus lower dose levels.

Results

The ratio of the clinically determined MTD to the starting dose for all 45 drugs on all schedules ranged from less than 1 to 433 (median, 20), and the number of dose-escalation steps required to reach the MTD ranged from 0 to 23 (median, 8; Tables 1 and 2). Only one drug, fludarabine (2-F-ara-AMP), began phase I study at a starting dose that exceeded the MTD. The dose-limiting toxicities for all drugs are shown in Table 2. In all, 25 drugs (represented by the letter N) caused nonhematologic dose-limiting toxicity and 18 (represented by the letter H) induced dose-limiting toxicity that usually manifested as leukopenia and/or thrombocytopenia. Two drugs, CI 941 and bisantrene, were associated with both kinds of dose-limiting toxicity.

The ratio of MTD to starting dose ranged from 3 to 385 (median, 30) for drugs with nonhematologic dose-limiting toxicity, and the number of dose-escalation steps ranged from 2 to 18 (median, 9). The MTDs of datelliptium, flavone acetic acid, and echinomycin far exceeded the starting dose. Datelliptium induced renal and hepatic dose-limiting toxicities when given on a daily $\times 3$ schedule, and the MTD was 385 times the starting dose. Flavone acetic acid caused dose-limiting hypotension, and the MTD was 100 times the starting dose. The MTD for echinomycin was 90 times the starting dose, and intractable vomiting was the dose-limiting toxicity. For 18 drugs with hematologic dose-limiting toxicity only, the ratio of MTD to starting dose ranged from less than 1 to 433 (median, 12.8), and the number of dose-escalation steps required to reach the MTD ranged from none to 23 (median, 5.5). Thrombocytopenia was dose-limiting for brequinar sodium given on a weekly schedule; the MTD was more than 400 times the starting dose, and 79 patients and 23 dose-escalation steps were required to achieve the MTD. For the daily $\times 5$ schedule, the MTD was at least 175 times the starting dose. The median MTD was 30 times greater than the starting dose for drugs with nonhematologic dose-limiting toxicity but was only 12.8 times greater for those with hematologic dose-limiting toxicity; this difference was significant ($P = 0.023$). Drugs with non-hematologic dose-limiting toxicity required an additional three to four dose-escalation steps to reach the MTD as compared with drugs whose toxicity was hematologic; this difference was also significant ($P = 0.038$). Only 1 of the 45 drugs (2.2%) began clinical study at a dose that exceeded the MTD.

In all, 29 responses were noted among 1,110 patients (2.6%) treated with 21 drugs in phase I studies. At the 3 highest dose levels, responses were reported for 17 of 476 patients (3.6%). Among the 634 patients treated at the lower dose steps, 12 responses were observed (1.9%). This difference was not significant ($P = 0.08$).

Discussion

These results document the inefficiency of conducting phase I studies using the customary approaches to initial dose selection and dose escalation. The median MTD for all 45 drugs on all schedules was 20 times greater than the starting dose and ranged from 1 to 433. The median MTD was 30 times greater than the starting dose for drugs with nonhematologic dose-limiting toxicity but was only 12.8 times greater for those with hematologic dose-limiting toxicity.

Both the starting dose and the escalation scheme must be considered in dealing with the issue of the safety and efficacy of phase I trials. It is clear from Table 2 that doubling the starting dose would have produced an initial dose that would have been generally as safe as that used in the studies we examined. The sole exception to this was fludarabine, which was toxic at the starting dose. Even tripling the starting dose would have resulted in an initial dose that would have been below the final MTD for all but four drugs (tiazofurin, 3-deazauridine, ICRF-187 on the daily $\times 3$ schedule and, again fludarabine). Although the starting

Table 2. Ratio of MTD to starting dose and number of dose-escalation steps required to reach the MTD

Number	Drug	Doselimiting toxicity	Schedule	Ratio of MTD to starting dose	Number of dose--escalation steps
1.	SM5887	H	Single dose every 3 weeks	13	7
2.	Deoxyspergualin	N	120-h CIV	34.9	10
3.	Amonafide	H	Single dose every 4 weeks	61.3	12
4.	Flavone acetic acid	N	Single dose every 3–4 weeks	100	14
5.	MZPES	N	Single dose	85.2	17
6.	Oxantrazole	H	Single dose every 3 weeks	9[a]	5[a]
7.	Menadiol	N	Single dose every 3 weeks	34[a]	10[a]
8.	Brequinar sodium (DUP785)	H	Weekly	433	23
			Daily ×5 every 4 weeks	175[a]	15[a]
9.	CI 941	H/N	Single dose every 3 weeks	162	13
10.	Carbetimer	N	Single dose every 4 weeks	47.2	11
11.	AZP	H	Single dose every 3 weeks	7	4
12.	3-Deazaguanine	N	Weekly ×3	66.7	12
13.	Acodazole	N	Single dose every 4 weeks	10	6
			Daily ×5 every 4 weeks	9	5
			120-h CIV	8	5
			Weekly ×4	59.2	12
14.	Didemnin B	N	Daily ×5	22.3	9
15.	Liblomycin	H	Weekly ×4	28	10
16.	Datelliptium	N	Daily ×3 every 3 weeks	385	18
			24-h CIV	12.5	6
17.	CB 10-277	N	Single dose every 3 weeks	75	13
18.	Didox	N	Single dose	39	11
19.	Ara-AC	H	72-h CIV	10	7
20.	KRN 8602	N	Daily ×3	12	5
21.	dFdC	H	Weekly ×3	35[a]	10[a]
22.	Trimetrexate	H	Single dose every 2 weeks	12	5
23.	Taxol	N	Single dose every 3 weeks	18	7
24.	Echinomycin	N	Single dose every 4 weeks	90	9
25.	Tiazofurin	N	Daily ×5	3	2
26.	Fludarabine (2F-Ara-AMP)	H	Daily ×5	<1	<0
27.	Aminothiadiazole	N	Daily ×3	16.7	8
28.	3-Deazauridine	H	Daily ×5	3	2
29.	L-Alanosine	N	Daily ×5	64	6
30.	Bisantrene	H/N	Single dose every 4 weeks	14	8
			Daily ×5	36	9
31.	ICRF-187	H	Daily ×3	3	4
			Daily ×5	7.5	5
32.	IMPY	N	Twice weekly ×3	18.2	9
			Daily ×5	10	4
33.	Mitoxantrone	H	Daily ×5	8	4
34.	PCNU	H	Single dose every 6 weeks	22	6
			Daily ×5 every 6 weeks	5	3
35.	Pentamethylmelamine	N	Single dose every 4 weeks	60	9
			Daily ×10	30	9
36.	Bruceantin	N	Weekly ×4	8.1	10
			Daily ×5	22.5	6
37.	Chlorozotocin	H	Daily ×5	16	5
38.	Indicine-N-Oxide	H	Single dose every 4 weeks	9	5
			Daily ×5	20	8
39.	PALA	N	Daily ×5	12.5	5
40.	AMSA	H	Single dose every 4 weeks	16	7
			Daily ×3	12.5	5
41.	Anguidine	N	Daily ×5	30	10
42.	Gallium Nitrate	N	Daily ×3	20	8
43.	Piperazinedione	H	Single dose every 4 weeks	24	7
44.	Maytansine	N	Single dose	66.7	9
			Daily ×3	50	9
45.	Pyrazofurin	N	Daily ×5	5	7

[a] MTD not final

H, Hematologic; N, nenhematologic; CIV, continuous i. v. infusion

dose of only 1 of the 45 drugs examined exceeded the MTD, the use of higher initial doses to save dose-escalation steps must be weighed against the risk of incurring potentially lethal toxicity.

Collins et al. [1, 2] have proposed a dose-escalation strategy based on the similarity of the area under the curve for plasma drug concentration times time (CXT) in humans at the MTD to the plasma CXT in mice at the LD_{10}. They retrospectively showed that a 20%–50% decrease in dose-escalation steps could be achieved for five drugs whose CXT ratio for the human MTD to the mouse LD_{10} was near unity. This approach has been prospectively validated for at least one drug [4]. A pharmacokinetically guided dose escalation is one approach to more efficient dosing in phase I trials. Potential difficulties include differences in drug metabolism between humans and mice and pharmacokinetic nonlinearity [3]. In addition, antimetabolite drugs that require nucleoside kinases for activation (dihydroazacitidine, fludarabine, and dideoxycytidine) may not be appropriate for this approach [2].

The use of the mouse LD_{10} for choosing starting doses and measuring plasma CXT places additional importance on the experimental determination of the LD_{10}. Difficulties in assessing mouse LD_{10}, LD_{50}, and LD_{90} values for antitumor drugs have been described elsewhere [6]. The LD_{10} can vary by greater than 100%, depending on the mouse strain, the vehicle in which the drug is given, and the route of administration. Such variability can be misleading in the selection of a starting dose and can contribute an added risk factor for the use of higher initial doses.

The statistical difficulties in determining a quantitative estimate of the MTD in humans have been described by Storer and DeMets [12], who noted that current phase I trial designs and analyses lack properties that would lead to an estimate of some desired percentile of the dose-toxicity curve and its standard error. Our analysis indicates that the starting dose of a new drug represents only a fraction of the MTD and that a large number of dose-escalation steps are required to determine the MTD. This is not efficient.

Although only a small number of patients showed responses in phase I trials, the majority who did were treated at or near the MTD. Other studies have reported that the majority of responses noted in phase I trials occurred at 80%–120% of the recommended dose for phase II studies [13]. The primary objective of phase I studies must also include rapid attainment of the MTD so that disease-oriented phase II studies can begin sooner. One approach would involve the use of pharmacokinetically directed dose-escalation schemes in phase I studies, especially for drugs predicted to induce nonhematologic dose-limiting toxicity in animal studies. This approach may allow phase II studies to begin earlier to identify potential therapeutic activity. Another approach would be to escalate doses by doubling them until grade 1 toxicity occurs and then to proceed with further dose escalation according to a conventional Fibonacci scheme. Finally, since the precision of the dose-toxicity relationship is limited by the small number of patients tested at each dose, phase I studies could be designed such that only a single patient is treated at a given doses level; on the occurrence of grade 1 toxicity, additional patients could be added to confirm toxicological observations (Von Hoff, personal communication).

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