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REVIEW

Lesley Seymour · Elizabeth Eisenhauer

A review of dose-limiting events in phase I trials: antimetabolites show unpredictable relationships between dose and toxicity

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Abstract *Introduction*: In a sample of NCIC CTG phase I trials we noted that studies of antimetabolites were frequently confounded by the occurrence of dose-limiting toxicities (DLT) at doses well below those ultimately recommended (recommended dose, RD) for further study, necessitating frequent expansion of dose levels and usually a change to more conservative dose escalation. This slowed development, exposed patients to ineffective doses of drugs, and raises concerns about the safety of current trial designs which include a single patient per dose level. Conversely, some patients treated at the RD may be receiving inadequate doses of anticancer drugs. To determine if this was a general phenomenon, we undertook a review of the results of a large group of phase I trials of cytotoxic agents. *Methods*: Starting dose (SD), number of dose levels, dose at first DLT (D-DLT), maximum tolerated doses (MTD, dose at which DLT is seen in two or more patients) and RD were extracted from the NCI-Canada phase I trial database, and from a literature survey of phase I studies published between 1985 and 1999. Combination phase I and phase Ib studies were excluded. *Results*: The review included 33 trials with antimetabolites and 60 with other cytotoxic agents. The median ratio D-DLT/MTD was 0.33 for antimetabolites and 0.75 for other cytotoxic agents ($P < 0.01$). Similarly, the median ratio D-DLT/RD was 0.43 for antimetabolites and 1 for other cytotoxic agents ($P < 0.01$). The median number of dose levels tested was nine for antimetabolites and six for other cytotoxic agents. *Discussion*: Statistically significant differences in the ratios D-DLT/MTD and D-DLT/RD between antimetabolites and other cytotoxic compounds were noted, confirming our initial observations that unpredictable DLT occurs earlier and at lower dose levels in phase I clinical trials of antimetabolites than would be expected as compared to other classes of cytotoxic agents. Toxicity thus appears to be incompletely predicted by dose alone for antimetabolites. DLT may occur in certain patients at doses well below the RD. Current phase I design may not be ideal for development of these compounds, and should focus on pharmacodynamic endpoints in addition to traditional pharmacokinetic and clinical endpoints.

Key words Antimetabolites · Dose-limiting toxicity · Endpoints · Phase I studies

L. Seymour (✉) · E. Eisenhauer
Investigational New Drug Program,
National Cancer Institute of Canada Clinical Trial Group,
Queens University, 18 Barrie Street,
Kingston, Ontario, K7L 3N6, Canada
e-mail: lseymour@ctg.queensu.ca
Tel.: +1-613-5336430

Introduction

A brief review of early-stage phase I clinical trials of antimetabolites conducted at the National Cancer Institute of Canada Clinical Trials Group suggested that dose-limiting toxicities (DLT) occurred at doses well below those ultimately recommended (recommended dose, RD) for further study, leading to the expansion of a number of dose levels and, usually, a change to a more conservative dose escalation. These preliminary observations seemed in contrast to those presented by Arbuck [1] in a recent phase I design workshop. In the National Cancer Institute (USA) database, the dose at first DLT (D-DLT) was 80% of the maximum tolerated dose (MTD). While a number of excellent reviews of phase I trial design have been published in the recent past [2, 3, 4, 5, 6, 7, 8], seeking to minimize the number of patients treated at subtherapeutic doses of drugs, and to improve speed and efficiency of trials whilst maintaining patient safety, most have not attempted to group compounds by therapeutic target. We were interested in exploring this observation further. Thus, we present a review of recently conducted phase I trials of cytotoxic agents from a variety of mechanistic classes and determined the doses at which DLT first occurred expressed as a ratio in relation to the RD. Since we hypothesized that this ratio would be lowest for antimetabolites, we compared the behavior of this class of drugs to that of all others.

Methods

Literature search

Medline was searched for all publications between 1985 and August 1999 including the following search terms: clinical trials, phase I; antimetabolites/antineoplastics; maximum tolerated dose; dose-limiting toxicity; dose escalation; dose ranging; antimetabolites; recommended dose; and phase I. Specific compounds were searched for by textword and by hand when referred to in other identified publications. Identified publications were considered suitable for inclusion if they included a full description of methodology including starting dose (SD), number of dose escalations and complete toxicity reporting. Only publications referring to cytotoxic compounds that were tested in solid tumors and in adult populations were included. Phase Ib studies and late phase I trials with starting doses determined by earlier work, with a limited number of dose levels or including combinations of drugs were also excluded, as were compounds abandoned whilst in phase I testing because of unusual or unmanageable toxicity.

Data collection

Data extracted from publications meeting the criteria defined above included trial design and methodology; definition of DLT (if included); schedule of drug administration; SD; MTD; RD; D-DLT; and when reported, impact of prior therapies on toxicity and RD; protein binding of the compound and impact of other demographic variables. For trials which defined different RDs and MTDs for heavily and lightly pretreated patients both sets of data were recorded if feasible and the separate cohorts had been formally tested; if not, only data from the cohort of patients for whom full data could be extracted were used. For trials testing different schedules and infusion lengths a similar approach was taken. Trials including different cohorts of patients or schedules were considered separately in the analyses and tables of results; thus two 'trials' may have the same reference.

Definitions

The term 'maximum tolerated dose' was variably defined in reports to indicate either the maximum dose tested, or the dose deemed tolerable and suitable for further study. In this report, we use MTD to indicate the maximum dose tested in the study, and RD to indicate the dose recommended for further study. When D-DLT was not clear, the most conservative interpretation was taken, except where otherwise indicated in the results.

Where DLT was not clearly defined in the report, the following definition was used: grade 4 neutropenia (or febrile neutropenia), grade 3 or 4 thrombocytopenia (or thrombocytopenic bleeding) or grade 3 or 4 nonhematologic toxicity. In some reports recommendations for dose reductions for a specific grade of toxicities were given, and these were used as the definition of DLT if not otherwise specified in the report.

Analyses

For each trial and for each compound (where more than one study was reported for a given compound) the ratios D-DLT/RD and D-DLT/MTD were calculated. The means and medians of protein binding, number of dose levels tested, D-DLT/RD and D-DLT/MTD for antimetabolites and other compounds were calculated. Testing for statistical significance was performed using Student's *t*-test (two-sided), after logarithmic conversion of the ratios. Note that in some studies, D-DLTs may have occurred at intermediate dose levels, i.e. those chosen after the MTD had been reached. For drugs associated with cumulative toxicities, sometimes different RDs and MTDs were defined for cycle 1 and continual treatment [77]; where appropriate the tables are annotated accordingly.

Results

Literature search

Over 400 citations were identified using the search terms and time frames specified in the methodology. On review of the abstracts of these citations, 208 appeared suitable for inclusion in this review. Of these, 185 reprints were retrieved. Papers were retrieved from journals that could be found at Queens University Health Science Centre Library or at NCIC CTG Library. Retrieval of papers from missing or unsubscribed journals at these libraries was not attempted.

Of the 185 full papers retrieved, 87 (including 93 different schedules or patient populations) were deemed suitable for inclusion in this review. Reasons for non-inclusion included: papers detailing pharmacokinetic results with only key clinical outcomes [9, 10]; trials in pediatric populations [11]; toxicity data presented incompletely [12, 13] or only at dose levels approaching RD; compounds (or schedules) with predominantly central [14, 15, 16, 17, 18] or peripheral nervous system toxicity [19] (diethylnorspermine, spirohydantoin mustard, BWA7704, high-dose edatrexate) or whose development was halted in phase I because of unusual toxicity [mafosfamide cyclohexamine [20] (local venous toxicity), LY186641 (methemoglobinemia), dezaguanine [21] (cardiotoxicity)]; and complex trials from which data were not easily retrievable [22].

The schedule, number of dose levels, SD, RD, MTD (highest dose tested) and D-DLT of compounds included in this review are detailed in Table 1 (17 antimetabolites in 32 trials) and Table 2 (35 other cytotoxic compounds in 60 trials). A summary of the median, mean, standard deviations and ranges of the D-DLT/RD and D-DLT/MTD ratios, and number of dose levels is presented in Table 3. For antimetabolites, D-DLT was reported at a median of 33% of the eventual MTD and a median of 43% of the eventual RD. A median of 9 dose levels were tested (2–24). There was no apparent difference between antifol antimetabolites and other antimetabolites, with the median D-DLT/RD being 0.45 and 0.49, respectively, and the median D-DLT/MTD being 0.37 and 0.36, respectively. For other cytotoxic compounds, D-DLT was reported at a median of 75% of the eventual MTD and a median of 100% of the eventual RD. A median of 6 dose levels were tested (2–24). These differences were highly statistically significant ($P < 0.01$). There was no apparent evidence that protein binding was higher for antimetabolites (62% versus 78%; Table 4).

Discussion

The observation that phase I studies of antimetabolites were often associated with intermittent, unpredictable toxicity at lower dose levels leading to prolonged and

Table 1 Antimetabolites (17 agents, 32 trials) (*BID* twice daily, *p.o.* by mouth)

Drug	Schedule	Number of dose levels	SD (mg/m^2)	RD (mg/m^2)	MTD (mg/m^2)	D-DLT (mg/m^2)	D-DLT/ RD ratio	D-DLT/ MTD ratio	Reference
10-EDAM	Weekly ×3	10	5	100	120	40[c]	0.4	0.33	33
5′-Deoxy-5-fluorouridine	Daily ×5	6	300	4000	5000	300[d]	0.075	0.06	34
BCH-4556	3-Weekly	13	0.025	10	12.5	4.8	0.48	0.38	35
Brequinar Na	Daily ×5	10	36	250	300	170	0.68	0.57	36
Brequinar Na[a]	Daily ×5	10	36	250	300	170	0.68	0.57	37
Brequinar Na[b]	Weekly	24	6	1500	2600	650	0.43	0.25	38
Brequinar Na[b]	Daily ×5	7	36	135	170	135	1.0	0.79	36
Capecitabine	BID ×14 days (p.o.)	6	502	2510	3514	1657	0.66	0.47	39
CB3717	3-Weekly	11	140	400	600	200[e]	0.4	0.33	40
CB3717	3-Weekly	6	50	400	400	50[e]	0.125	0.125	41
Dichloromethotrexate	Weekly ×3	5	400	785	980	400	0.51	0.41	42
Fazarabine	3-Day infusion	12	4.8	48	144	10	0.2	0.07	43
Gemcitabine	Weekly ×3	13	10	790	1000	525	0.67	0.53	44
Gemcitabine	2-Weekly	14	40	4560	5700	960	0.21	0.17	45
Gemcitabine	24-h infusion	7	10	180	210	40	0.22	0.19	46
Lometrexol	Weekly ×3	3	3	6	6	4.5	0.75	0.75	47
LY231514	Weekly ×4	4	10	30	40	10	0.33	0.25	48
LY231514	Daily ×5	10	0.2	4	5.2	2.3	0.58	0.44	49
Nolatrexed	Daily ×5	9	96	800	1040	432	0.54	0.42	50
Nolatrexed	Daily ×5 (p.o.)	4	288	800	1000	576	0.72	0.58	51
Piritrexim[f]	Weekly ×4	7	44	400	530	148	0.37	0.28	52
Raltitrexed	3-Weekly	10	0.1	3	3.5	2.6	0.87	0.74	53
Tiazofurin	Daily ×5	4	550	1100	2200	1100	1.0	0.5	54
Trimetrexate	Daily ×5	12	0.5	8	15	3.1	0.39	0.21	55
Trimetrexate	5-Day infusion	6	1	8	12	10	1.25	0.83	56
Trimetrexate	24-h infusion	6	16	150	200	32	0.21	0.16	57
Trimetrexate	2-Weekly	13	5	200	450	20	0.1	0.04	58
Trimetrexate	Weekly ×3	6	50	100	200	50	0.5	0.25	57
Trimetrexate	3-Weekly	9	20	220	275	90	0.41	0.33	59
ZD9331[f]	3-Weekly	12	4.8	370	370	48	0.13	0.13	60
ZD9331	Daily ×5	11	0.4	12	16	4.8	0.4	0.3	61
ZD9331	Weekly ×2	10	4.8	130	162	32	0.25	0.2	62

[a] Lightly pretreated/good risk group
[b] Heavily pretreated/poor risk group
[c] Transaminase elevation, dose level expanded
[d] Patient died of thrombocytopenic bleeding
[e] Based on nephrotoxicity
[f] MTD not actually reached/schedule not taken forward

delayed development spurred this retrospective literature review. Phase I trials that include a large number of patients at many dose levels are problematic for a number of reasons: drug development time is prolonged, leading to delayed availability of a potentially useful compound, and many patients are exposed to the agent at what subsequently proves to be subtherapeutic doses. Conversely, accelerated phase I designs utilizing dose-doubling strategies, or a single patient per dose level, may expose some patients to excessive toxicity.

Although it was attempted to make this review as comprehensive as possible, it is likely that some phase I studies of compounds that were not developed further were not published. Some, particularly older, publications reported summarized toxicity data which were not always complete, especially at the lower dose levels. It was not always clear whether the toxicity data presented represented all cycles administered, or cycle 1 toxicity data only. It was unusual to have cycle 1 and subsequent cycles presented separately. Only a limited number of studies attempted to correlate toxicity with clinical variables such as liver function or protein levels, and only a handful correlated toxicity with other correlates such as nutritional status. Not all studies published during this time period were included, for example if they were complex in design, such as the lometrexol phase I studies in combination with folinic acid, or were late phase I in design with MTD and RD already having been defined in earlier work.

Despite these limitations, it appears that antimetabolites are indeed more likely to be associated with sporadic DLT at doses sometimes substantially below those eventually declared as the RD for further study. This effect is not confined to subgroups of antimetabolites, and is seen with antifols to the same degree as with other antimetabolites. Further, the median number of dose levels tested was significantly higher for antimetabolites than for other cytotoxic compounds (nine vs six dose levels). There was no evidence that protein binding, where the data were available, was higher for antimetabolites.

Murine models are not ideal for assessing toxicity of antimetabolites, especially thymidylate synthase-based

Table 2 Other cytotoxic compounds (35 agents, 60 trials) (*p.o.* by mouth, *9-AC* 9-amino-camptothecin)

Drug	Schedule	Number of dose levels	SD (mg/m^2)	RD (mg/m^2)	MTD (mg/m^2)	D-DLT (mg/m^2)	D-DLT/ RD ratio	D-DLT/ MTD ratio	Reference
9-AC	24-h infusion	4	0.7	1.65	1.9	1.65	1.0	0.87	63
9-AC[a]	72-h infusion	7	120	1080	1440	1080	1.0	0.75	64
4′-Deoxydoxorubicin	3-Weekly	6	10	30	35	30	1.0	0.86	65
Ametantrone	Daily ×5	4	15	30	35	30	1.0	0.86	66
Amonafide[b]	Daily ×5	9	10	320	400	320	1.0	0.8	67
Amonafide	4-Weekly	9	18	918	1104	800	0.87	0.73	68
Carboplatin[c]	4-Weekly	9	20	400	600	270	0.68	0.45	69
Carboplatin[b]	4-Weekly	8	20	270	500	120[d]	0.44	0.24	68
Carboplatin	4-Weekly	6	40	400	440	320	0.8	0.73	70
Carzelesin[a]	Daily ×5	5	12	35	40	24	0.69	0.6	71
Carzelesin[a]	4-Weekly	9	24	150	170	96	0.64	0.56	72
CI-921	Daily ×3	9	13	216	270	216	1.0	0.8	73
CI-973[b]	Every 4 weeks	6	75	190	230	150	0.79	0.65	74
CI-980	72-h infusion	4	3	3.75	5.4	4.5	1.2	0.83	75
CI-980	24-h infusion	8	1.2	10.8	15.6	10.8	1.0	0.69	76
Chlorozotocin	Weekly ×4	9	10	40[e]	120	60	1.5	0.5	77
CPT-11	3-Weekly	6	100	240	345	240	1.0	0.70	78
Diazaquinone	5-Day infusion	3	4	6	8	6	1.0	0.75	79
DMP 840[c]	3 Weekly	5	8	60	80	80	1.3	1.0	80
DMP840	24-h infusion	4	20	40	60	50	1.25	0.83	81
Docetaxel	Daily ×5	6	1	14	16	12	0.86	0.75	82
Docetaxel	24-h infusion	6	10	70	90	90	1.29	1.0	83
Docetaxel	Weekly ×2	6	10	50	65[f]	50	1.0	0.77	84
Docetaxel[c]	2–6-h infusion	8	5	100	115	80[c]	0.8	0.7	85
DUP-937	Weekly	10	0.55	12.3	16	12.3	1.0	0.77	86
GI147211[c]	Daily ×5	6	0.3	1.5	1.75	1.75	1.17	1.0	87
GI147211[c]	72-h infusion	7	0.25	1.75	2.5	2	1.14	0.8	88
GI147211[b]	Daily ×5	5	0.3	1.0	1.5	1.2	1.0	0.8	87
GI147211[b]	72-h infusion	6	0.25	1.2	2.0	1.5	1.25	0.75	87
GI147211	Daily ×5	5	0.3	1.2	1.5	1.2	1.0	0.8	89
Iproplatin	Weekly ×4	5	40	95	120	60	0.63	0.5	90
JM216[b]	Daily ×14 p.o.	6	10	40	45	30	0.75	0.67	91
JM216[b]	Daily ×5 p.o.	5	30	100	140	30[d]	0.25	0.21	92
KRN8602[g]	3-Weekly	5	10	40	50	40	1.0	0.8	93
LU103793	Daily ×5	5	0.5	2.5	3	2	0.8	0.67	94
Menogaril	Daily ×5	8	3.5	50	56	50	1.0	0.89	95
Menogaril[c]	Weekly ×2	8	9	140	140	140	1.0	1.0	96
Menogaril[b]	Weekly ×2	7	8	90	112	72	0.8	0.64	95
Mitozolomide	6–8-Weekly	9	8	115[h]	153	125	1.1	0.82	97
NK611[i]	Daily ×21 p.o.	4	5	10	15	10	1.0	0.67	98
N-Methylformamide	Weekly ×3	9	125	2000	3125	1500	0.75	0.48	99
N-Methylformamide	Weekly ×6	4	875	1125	2000	1125	1.0	0.56	100
Oxaliplatin	3-Weekly	7	45	135	200	135	1.0	0.68	101
Piroxantrone	3-Weekly	9	7.5	150	190	120	0.8	0.63	102
PK-1	3-Weekly	8	20	280	320	320	1.14	1.0	103
Rhizoxin	Every 3 weeks	4	0.8	2	2.6	2	1.0	0.77	104
RPR 109881A	Weekly ×2	7	7.5	45	52.5	52.5	1.17	1.0	105
S10036	Weekly ×4	8	25	100	200	82.5	0.83	0.41	106
TCNU[j]	5-Weekly p.o.	12	10	130	150	70	0.54	0.47	107
TCNU[c]	4–5-Weekly p.o.	10	20	130	170	90	0.69	0.53	107
TCNU[b]	4–5-Weekly p.o.	7	20	90	110	70	0.78	0.64	108
TGU	4-Weekly	10	30	800	900	800	1.0	0.89	109
TGU	Daily ×5	8	6	200	250	200	1.0	0.8	110
Titanocene	3-Weekly	9	15	240	315[k]	240	1.0	0.76	111
Titanocene	Weekly	5	70	140	185	140	1.0	0.76	112
Topotecan	Daily ×5	6	0.5	1.5	0.9(1.5)[l]	0.9	0.6	0.6	113
Topotecan	Daily ×21 p.o.	5	0.3	1	1.2	0.8	0.8	0.67	114
Topotecan[c,g]	Daily ×5	5	0.5	1.5	1.75	1.75	1.16	1.0	115
Topotecan[b,g]	Daily ×5	4	0.5	1.25	1.5	1.5	1.2	1.0	115
Vinzolidine	Daily ×3	4	2	3	4	3	1.0	0.75	116

[a] $\mu g/m^2$
[b] Heavily pretreated/poor risk group
[c] Lightly pretreated/good risk group
[d] Heavily pretreated patient with Hodgkin's disease
[e] Based upon cumulative toxicity
[f] No patients received full cycle at this dose level
[g] Dose levels using hematologic growth factors not included
[h] RD based on other studies was 90 mg/m^2
[i] Flat dose, not given by BSA
[j] Excludes unpremedicated nausea and vomiting
[k] Higher dose were tested but criteria for MTD met
[l] Dose escalated past protocol MTD

Table 3 Median, mean, standard deviations and ranges for D-DLT/RD and D-DLT/MTD for antimetabolites and other cytotoxic compounds

		Median	Mean	Range	Standard deviation
Antimetabolites	D-DLT/MTD	0.33	0.36	0.06–0.83	0.176
	D-DLT/RD	0.43	0.49	0.07–1	0.222
	Dose levels	9	8.84	2–24	4.26
Other cytotoxic compounds	D-DLT/MTD	0.75	0.73	0.21–1	0.217
	D-DLT/RD	1	0.94	0.25–1	0.282
	Dose Levels	6	6.63	3–12	2.025

Table 4 Known pharmacogenetic variations in pharmacology of antineoplastic agents

Enzyme	Action	Abnormality	Presentation
Thiopurine *S*-methyl transferase	Inactivates 6-mercaptopurine by *S*-methylation	Inactivating mutations or ethnic-/age-related variation in activity	Intolerance to 6-MP or resistance to treatment with 6-MP
Dihydropyrimidine Dehydrogenase	Catalyzes 5-fluorouracil catabolism	Autosomal recessive DPD deficiency; high levels of expression may be associated with drug resistance	Intolerance to 5-FU, resistance to treatment with 5-FU
CYP3A4, CYP3A5, CYP3A7	NB in metabolic pathways of a number of drugs	Known substrates include ifosfamide, cyclophosphamide, vincas and paclitaxel	Unknown
Glutathione-*S*-transferases	Inactivates alkylating agents by conjugation with glutathione	High levels associated with drug resistance	Drug resistance
N-Acetyltransferase-2	Acetylation of amonafide	Fast acetylators accumulate myelosuppressive metabolites	Increased toxicity in fast acetylators
Uridine diphosphate glucuronsyltransferases	Conjugates drugs (irinotecan) to form glucuronides	Crigler-Najjar and Gilberts syndrome	Increased diarrhea due to increased biliary excretion of SN-38

compounds due to high circulating thymidine levels [23]. Such interspecies differences may result in difficulties in predicting DLTs and the definition of an appropriate SD, as well as in clearly delineating toxicokinetic relationships prior to the initiation of clinical studies.

The majority of drugs mentioned here based dosing upon body surface area (BSA), which is recognized as a crude determinant of optimal dosing [24, 25, 26]. Genetically determined differences in drug-metabolizing enzymes and targets (enzymes or receptors) are a well-described cause of variability in effects of drugs and may affect drug activation/biotransformation, metabolism, detoxification and excretion (Table 4) [27, 28]. Although pharmacogenetic effects are not confined to antimetabolites, it is feasible that antimetabolites may be subject to a number of different pharmacogenetic variables which together result in higher interpatient variability compared to other classes of compounds.

Age, organ function, obesity and hypoproteinemia may all play a role in interpatient variability in drug handing. Many drugs, including antimetabolites and other cytotoxic agents have toxicity correlates with determinants other than BSA. Such drugs include carboplatin and topotecan (renal function), etoposide (hepatic and renal function, hypoproteinemia), docetaxel (BSA plus age, hypoproteinemia, hepatic function), anthracyclines and vinca alkaloids (hepatic function), 5-fluorouracil (age) and busulfan (hepatic function and age).

A number of studies have been reported demonstrating specific correlations with toxicity. Johnson et al. reported a population pharmacokinetic analysis of LY231514, and described a correlation between pharmacokinetic parameters and clearance, creatinine clearance, body weight, alanine transaminase and folate status, with folate deficiency defined as homocysteine >13.9 μM, cysteine >342 nM and methylmalonic acid >73 nM and <271 nM [29]. Niyikiza et al. described a correlation between baseline homocysteine levels and the development of LY231514-induced grade 4 hematologic and grade 3 or 4 gastrointestinal toxicities [30]. Jackman et al. described a correlation between plasma 2′-deoxyuridine and myelosuppression for patients treated with ZD9331, a quinazoline antifolate; this may prove to be a useful pharmacodynamic marker [31]. Eisenhauer et al. identified low pretreatment serum protein levels and metastatic liver disease as significant correlates of severe toxic effects after trimetrexate administration, noting that trimetrexate is extensively protein bound and is cleared primarily by hepatic metabolism [32].

Thus, although antimetabolites appear to be associated with substantially more interpatient variability resulting in prolonged phase I development than other cytotoxic compounds, the etiology is unclear, although early work suggests that for antifols at least nutritional factors such as folate pools and protein levels may play a role.

Whilst it is encouraging to note that in recently conducted clinical trials attempts have been made to include pharmacodynamic endpoints and measures of target into the objective of the trials, it is likely that routine inclusion of relevant pharmacodynamic endpoints into phase I trials will increase the efficiency of clinical trials of antimetabolites as well as optimize dosing for individual patients, ensuring that active doses of drugs are administered and that the number of patients exposed to toxic doses of drugs is minimized. To facilitate this, consideration should be given to including correlative studies of toxicity with relevant variables (for example, nutritional status) in preclinical toxicology studies, but recognizing the difficulty of this for certain compounds such as antifol antimetabolites in murine models. In light of the demonstration of these consistent patterns of interpatient variability in toxicity after exposure to antimetabolites, current rapid-escalation trial designs in which a single patient is enrolled to a dose level may not be appropriate.

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