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Response rates, duration of response, and dose response effects in phase I studies of antineoplastics

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Summary

Over a period of 14 years, 7,960 patients were treated in 228 phase I trials. In these patients, there were 75 complete and 432 partial responses for an overall objective response rate of 6%. Complete responses lasted a median of six months (range 1–18), while partial responses lasted a median of three months (range 1–17). Of note is that no drug has made it to the market which has not had a response in phase I trials. Responses were noted in very diverse histologic types of tumors. Although there were responses at doses which were as low as 3–5% of the recommended dose for phase II trials, the majority of responses did occur at 80–120% of the dose recommended for phase II trials. Although the response rate in phase I trials is indeed low, responses do occur. This response rate information should help the clinician provide facts for the patient considering a phase I trial with new anticancer agents. These findings also emphasize that although phase I trials are characteristically dose-finding studies, if no responses are noted in phase I studies, it is unlikely the drug will be used routinely in the clinic.

Introduction

When an oncologist approaches the patient to present the possibility of receiving a new anticancer agent in a phase I trial, he should be able to tell that patient what the chances are the patient will benefit from this new agent. Even though phase I trials are supposed to be dose-finding studies, both the physician and the patient are hoping the drug will demonstrate some antitumor activity for the patient. Unfortunately, no antitumor activity data will be available on the new agent because it is of course an unknown. However, another approach is to look at the question from an historical perspective (i.e., what has been the objective response rate for patients receiving investigational new drugs in phase I studies?). A second question is whether those responses were achieved at or near the dose recommended for phase II trials or were responses seen even at lower doses which did not manifest any other biologic effect?

The purpose of the present study was to examine these two questions based on a review of phase I trials over a 14 year period of time. The years 1970–1983 were chosen because this was a homogeneous period in drug development during which the National Cancer Institute was sponsoring essentially all new agent development in a uniform manner.

Materials and methods

All major cancer journals from the years 1970–1983 were searched for phase I trials with new antineoplastic agents. Medline, Cancer line and Toxline were also consulted. Only published trials in the form of complete studies were utilized. No abstracts of phase I trials were included in the analysis. A total of 228 phase I studies were examined,

which included trials with 113 *different* agents.

The following parameters were collected for each study: (1) number of patients entered into each study; (2) the maximum tolerated dose; (3) the dose recommended for phase II studies; (4) the number of complete, partial, and marginal responses and the number of patients with stable disease; (5) the dose of drug at which the responses for each patient occurred; (6) the type of tumor the responding patients had; and (7) the duration of the responses.

As definitions of response for solid tumor patients, we utilized standard Southwest Oncology Group criteria which included:

1. **Complete remission**, defined as disappearance of all clinical evidence of active tumor for at least four weeks. The patient must be free of any symptoms related to the malignancy.
2. **Partial remission**, defined as 50% or greater decrease in the sum of the products of the diameters of the measured lesions for at least three months. No simultaneous increase in size or appearance of new lesions may occur.
3. **Stable disease**, defined as steady state or with a decrease in disease of $<25\%$, or an increase in disease that is less than progression. There may be no appearance of new lesions and no worsening of symptoms. This state must be maintained for a minimum of three months.
4. **Progression**, defined as unequivocal increase of at least 50% in the size of any measurable lesion, the appearance of new lesions, uncontrolled hypercalcemia or increasing skeletal involvement as manifested by an increasing number of lytic lesions or lesions on bone scan.
5. A final category which is included in standard Southwest Oncology Group Criteria is the category of a marginal response. Marginal response is defined as any decrease in tumor size of from 25–49% in the sum of the products of the diameters of the measured lesions for at least three months. This is not usually utilized as any meaningful measurement of response and is often included in the definitions of stable disease. However, many phase I investigators reporting their data have used this category so the information was collected.

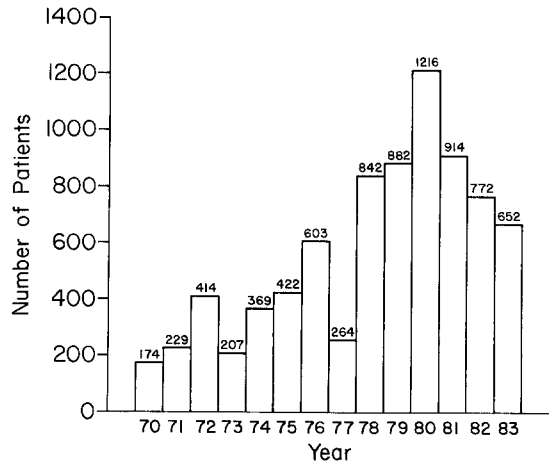

Fig. 1. Number of patients in published phase I trials each year from 1970–1983.

For definitions of response for patients with leukemia, standard Southwest Oncology Group criteria were also utilized.

Results

Overview

A total of 7,960 patients were treated in the 228 phase I studies examined. Figure 1 details the number of patients entered on phase I trials each year. A maximum of 1,216 were reported on phase I trials in 1980. This number has decreased since then. Over the 14 years surveyed, an average of 569 patients were entered on phase I trials each year. The drugs studied each year are detailed in Table 1. The average number of *different* drugs studied per year was 13 (range 2–26).

The number of responses, as well as the number of patients with stable disease, recorded each year are listed in Table 2. Overall, for the 7,960 patients treated, there were 75 complete responses and 432 partial responses for an overall objective response rate of 6.3%. If the 228 marginal responses are included, the overall response rate is 9.8%. As noted in Table 2, the yearly percent complete plus partial response ranged from 2% to 31%. Table 3 details the duration of the responses. The duration for complete and partial responses was quite respectable in these patients with advanced disease.

Table 1. Drugs studied in phase I trials each year

Year	Compounds studied in phase I trials during year
1970	Adriamycin
	Emetine
1971	DTIC
	CCNU
	Dibromodulcitol
	Pseudourea
1972	4′-demethylepipodophyllotoxin
	DTIC
	5-Azacytidine
	Thiosemicarbazone
	Bleomycin
	Camptothecin
	Methyl CCNU
	Porfiromycin
	TEPA 132
1973	Chromomycin A_3
	Cisplatinum
	ICRF-159
	Tilerone
1974	4′demethylepipodophyllotoxin
	5-Azacytidine
	BCNU
	Cisplatinum
	ICRF-159
	Lapachol
	Vitamin A
1975	5-Azacytidine
	C. Parvum
	Cyclocytidine
	Ftorafur
	Guanazole
	Inosine dialdehyde
	Isophosphamide
	L-asparaginase
	Porfiromycin
	Thalicarpine
	Yoshi 864
1976	Dianhydrogalacitol
	Anhydro-ara-5-fluorocytidine
	Bakers Antifol
	Chromomycin A_3
	Cytembena
	DTIC
	Levamisole
	Maytansine
	Mitomycin-C (oral)
	VP16-213
1977	Carmimomycin
	Cisplatinum
	MER-BCG
	Pyrazofurin
1978	Aclacinomycin A

Table 1. Continued

Year	Compounds studied in phase I trials during year
	AMSA
	Anguidine
	Chlorozotocin
	C. Parvum
	Gallium nitrate
	Hycanthone
	Levamisole
	AMSA
	Maytansine
	Methotrexate
	Misonidazole
	N-Benzyladenosine-5′-monophosphate
	Neocarzinostatin
	Pseudomonous Vaccine
	Pyrazofurin
	Quelamycin
1979	4′epi-adriamycin A
	Aclacinomycin A
	Glutaminase
	Aminopterin
	Anguidine
	Bruceantin
	Chlorozotocin
	Gallium nitrate
	Hycanthone
	IMPY
	AMSA
	Maytansine
	MER-BCG
	PALA
	Neocarzinostatin
	Piperazinedione
	Quelamycin
	Streptozotocin
	Thymidine
	Vincristine
	VP16
1980	HCFU
	3-deazauridine
	5FU
	DON
	Aclacinomycin A
	AMSA
	Glutaminase
	Carminomycin
	Chlorozotocin
	Cisplatinum
	C. Parvum
	Mitoxantrone
	Fibroblast interferon
	IMPY
	AMSA

Table 1. Continued

Year	Compounds studied in phase I trials during year
	Malanotoplatinum
	Metoprine
	M. Smegmatis cell wall
	PALA
	PCNU
	Pentamethylmelamine
	Pseudoisocytidine
	Quelamycin
	Glutaminase
	Spirogermanium
	Vinblastine
	Vindestine
	WR2721
1981	2-deoxycoformycin
	5-aza-2′deoxcytidine
	5FU
	Aclacinomycin A
	AD32
	Ametantrone
	AZQ
	Bisantrene
	Bruceantin
	Nocardia rubra cell wall
	Chlorozotocin
	Mitoxantrone
	DON
	ICRF-187
	IMPY
	Misonidazole
	PCNU
	Pentamethylelamine
	Rubidazione
	Vincristine
	Vindesine
	VP16
	Immune RNA
1982	Carboxyphtalatoplatinum
	4-demethoxydaunorubicin
	5′-deoxy-5-fluororidine
	13-cisretinoic acid
	DON
	9-hydroxy-2Nmethyl-ellipticinium acid
	Acivicin
	Aclacinomycin A
	Adriamycin
	Bisantrene
	Carminomycin
	Cisplatinum
	Doxorubicin-DNA-complex
	Human lymphoblastoid interferon
	Indicine-N-oxide
	L-Alanosine

Table 1. Continued

Year	Compounds studied in phase I trials during year
	Methy GAG
	Mitomycin
	Mitoxantrone
	Pentamethylmelamine
	SOAZ
	Spirogermanium
	StaphAureus
	VP16
1983	10-deazoaminopterin
	4′-O-tetrahydropyranyl
	4-demethoxydaunorubicin
	Aclacinomycin A
	Aclarubicin
	AZQ
	Indicine-N-oxide
	L-Alanosine
	Marcellomycin
	Mitoxantrone
	MVE-2
	Pepleomycin
	Alpha 2 interferon
	Retinal
	Semustine
	SOAZ
	Spirogermanium
	Tegafur
	Tricyclic nucleoside phosphate

Table 4 details the types of tumors patients had which responded (in which the tumor types were detailed). It is clear that although no denominators are known for most of the studies, there is indeed a diversity in histologic types of tumors which responded in these studies.

The next question was whether or not a response in phase I trials was of prognostic significance for the drug to be successful (i.e., make it to the market). Figure 2 details the number of responses in phase I trials for drugs that made it to the market (or will be on the market within the next year) versus those drugs which will definitely not be marketed versus those in which the marketing strategy is not yet clear (i.e., still under active investigation). As noted in Fig. 2, the range of number of responses in phase I trials is quite great for both marketed and non-marketed drugs. The median number of responses is higher (six total responses)

Table 2. Number of responses each year in phase I clinical trial

Year	Total patients treated	#CR	#PR	#MR	#Stable	%CR + %PR
1970	174	7	47	17	2	31
1971	229	4	27	0	60	14
1972	414	8	64	8	15	17
1973	207	12	14	7	1	13
1974	369	3	4	17	14	2
1975	422	2	19	5	0	5
1976	603	1	19	17	19	3
1977	264	1	19	12	2	8
1978	842	4	33	14	33	4
1979	882	5	32	40	59	4
1980	1216	6	64	64	67	6
1981	914	15	35	29	25	5
1982	772	2	29	31	53	4
1983	652	5	26	17	42	5
Totals	7960	75	432	278	393	–

Table 3. Duration of responses in phase I studies

Type of response	Duration of response (months)	
	Median	Range
Complete	6	1–18
Partial	3	1–17
Marginal	3	1–18
Stable	4	1–36

for those compounds which eventually were marketed versus those that were not marketed (one total response). To date, there has not been one compound which has made it to market which did not have at least one response in phase I trials.

Another major question in phase I trials is whether a patient must receive a dose near the dose recommended for phase II trials with the agent in order to have a response. Figure 3 details the percent of the recommended phase II dose at which the responses in phase I trials occurred. From this figure, it is quite clear that there is considerable variation in the percent of the recommended dose at which responses or stable disease occur. Complete and partial responses were noted even at doses as low as 3–5% of the recommended dose. It is of interest that when the medians are examined, it does appear that the closer one is to 100% of the recommended phase II dose, the better the chances of achieving a complete, partial, or marginal response. Patients with stable disease received less of a dose (on the median).

Figure 4 examines the data in another way. In that figure, the distribution of response, according to percent of recommended phase II doses is plotted for each of the response and stable disease categories. It is clear from that diagram that the greatest percentage of responses (complete, partial or marginal) were noted in the category of 80–120% of the recommended dose for phase II trials. However, the stable disease patients exhibited no such distribution of responses.

Discussion

The first finding of this study is that in the 228 phase I studies conducted in 7,960 patients over the 14 year-period, the overall percent of objective responses was 6% (1% complete response and 5% partial response). The 6% response is higher than the 2% response rate noted by Estey and colleagues [1] when they examined the response rate in a smaller number of patients (1,248) in phase I clinical trials. If we examine the response rate by year, there is no indication that the response rate is im-

Table 4. Types of tumors in which objective responses occured

Tumor type	Number of completed responses	Number of partial responses
Acute lymphocytic leukemia	13	15
Acute non-lymphocytic leukemia	10	20
Adrenal	–	1
Anus-squamous	1	3
Brain	–	15
Breast	1	30
Bladder	2	4
Carcinoid	1	2
Cervix adenocarcinoma	–	1
Cervix-squamous	1	10
Choriepothelioma-uterus	–	1
Choriocarcinoma	–	1
Clear cell – Vagina	–	1
CLL	2	2
Colorectal	2	29
Esophagus	–	1
Fallopian tube	–	1
Gastric	2	14
Head and neck	6	21
Hepatoma	–	5
Lung		
Small cell	1	8
Non-small cell	2	39
Lymphoma		
Hodgkin's	1	20
Non-Hodgkin's	7	49
Melanoma	1	3
Mycosis fungoides	1	3
Myeloma	–	1
Neuroblastoma	–	4
Ovary	1	13
Pancreas	–	1
Prostate	–	1
Renal	3	10
Sarcoma	2	35
Teratoma-Mediastinum	–	1
Testes	7	13
Thymus	1	2
Thyroid	1	3
Unknown primary	1	19
Uterus	–	1

proving. In fact, in 1972 with only two drugs studied, the response rate in phase I trials was 31% (Adriamycin was in phase I trials that year), while in 1983, the phase I trial response rate was only 5%. This trend, plus the large inflation in number of patients entered into phase I trials in the late 1970's

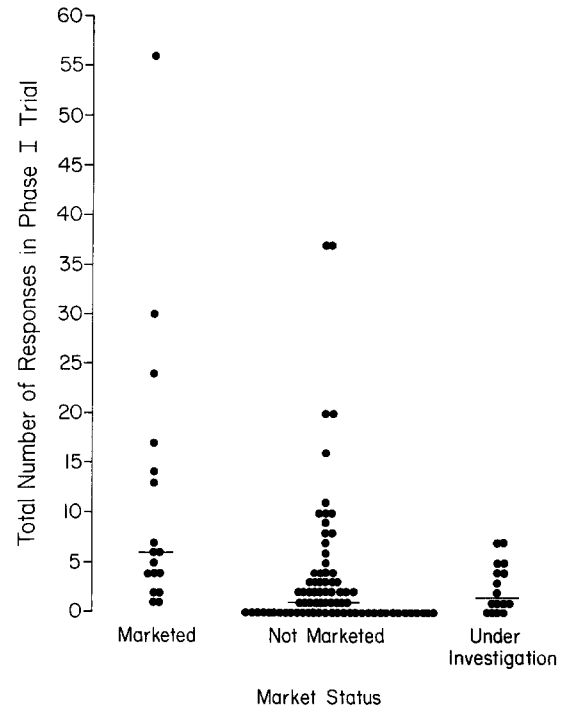

Fig. 2 Number of responses in phase I trials for marketed, non-marketed, and for drugs still under investigation. Lines represent median number of responses. These values are six total responses for marketed compounds, one for non-marketed compounds, and 1.5 responses for those still under investigation.

and early 1980's, make it possible to speculate that drugs may not have been selected as carefully for phase I trials. Keeping track of this trend is indeed important as this information can provide input into the screening programs utilized by the National Cancer Institute. This is particularly important as the NCI changes its screen [2,3]. In addition, with the very low response rates in phase I trials, it appears that there may be room for the addition of a screening method for the patients. Perhaps as the methodology for *in vitro* sensitivity testing becomes more refined, patients with tumors sensitive *in vitro* can be selected for entrance into phase I studies with an attendant improvement in response rate [4,5,6]. If nothing else, the present study will serve as an historical benchmark against which to assess changes in the drug screen or changes in the patient screen.

The overall clinical response rate of 6% in the phase I studies is of course not very encouraging,

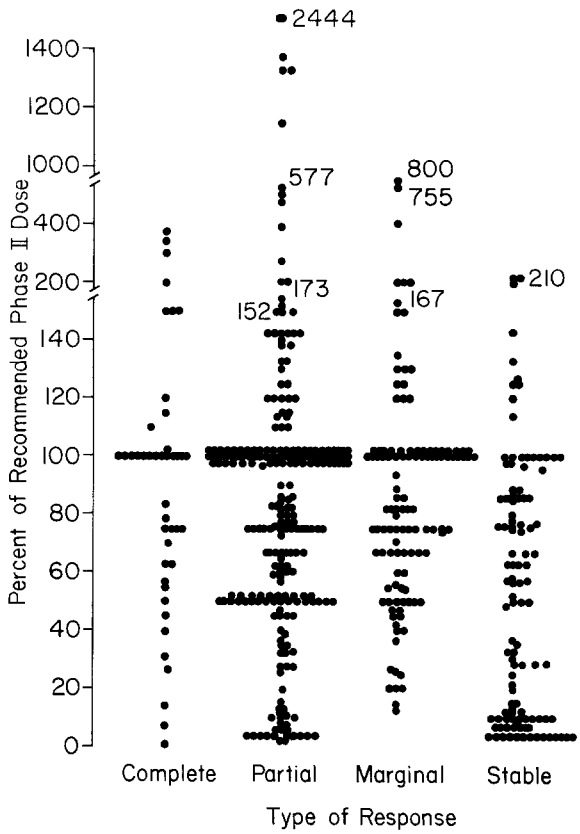

Fig. 3. Distribution of percent of phase II recommended dose at which complete, partial, and marginal responses, as well as stable disease, were noted in phase I trials. Each point represents one response. Median percentage of recommended phase II doses at which responses occurred were 100% recommended phase II doses for complete responses, 84% for partial responses, 86% for marginal responses, and 49% for stable diseases.

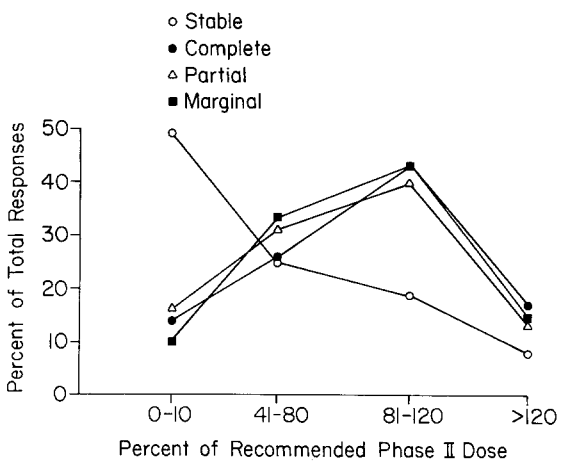

Fig. 4. Distribution of percent of total responses in phase I study according to percent of recommended phase II doses.

particularly when a background response of 10% might be anticipated by measurement error alone [7]. However, the responses noted in the phase I studies were reasonably durable (median 3–6 months). In addition, responses were noted in a diverse group of tumor types, including some very rare malignancies. This finding is somewhat surprising since it is generally felt most responses in phase I trials are noted in patients with leukemia and lymphoma. The finding of a 6% overall response rate in phase I studies is particularly interesting when compared to overall response rates for phase II studies in untreated patients with non-small cell lung cancer. In a very fine analysis, Pazdur and colleagues noted only a 4% response rate in those patients. It appears those patients might have had as much of a chance for response if they had been offered a phase I agent [8].

Although some responses were noted at doses far below the doses eventually recommended for phase II trials with the new agent, the majority of responses did occur at 80–120% of the dose recommended for phase II studies. There did appear to be more complete, partial, and marginal responses at the higher doses. Therefore, it is clear that the patient's best chance for response is at the higher dose levels. This finding should intensify our efforts at developing new, more rapid escalation schemes to improve the patient's chance for response, but preserve the safety of the study.

Of additional interest was the finding that all of the agents which have made it to the market have had a median of six responses noted in the phase I studies of the agent. Objective responses in the phase I study did not of course guarantee successful marketing of the agent. However, if no responses are noted in a phase I trial, the present study shows it has a low probability of being marketed (i.e., of being useful in the clinic).

Hopefully, the findings of this study will help the clinician who is trying to present the phase I option to the patient. There is a small but finite chance of response for patients with a wide variety of malignancies. Responses are noted at low doses, but chances for response are better at the high doses. If a response is achieved, it will last (on the median) three to six months.

Acknowledgement

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