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Clinical report

Patients who are receiving concomitant medications should not systematically be excluded from phase I studies

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This retrospective study was designed to evaluate possible relationships between the number and types of concomitant medications administered to patients on the first day of therapy in phase I trials and demographic characteristics, outcome measures and toxicities. Concomitant medications received by 690 patients enrolled on 28 phase I trials between August 1985 and January 1996 were grouped into 31 categories based on the American Hospital Formulary Service 1993. These patients received 1650 cycles of treatment with investigational agents (median 2 cycles per patient). Median duration on-study was 49 days (range 1–776 days). Clinical response rate (complete, partial, minor) was 3.8%. Only three toxic deaths occurred (0.4%). Nearly all patients (90.9%) received at least one concomitant medication on the first day of therapy. The number of concomitant medications directly correlated with poor performance status (r_{Sp}=0.27, p<0.0001) and indirectly with duration on-study (r_{Sp}=−0.18, p<0.0001). The dose of the investigational agent administered during the first course of therapy was not related to concomitant medications on the first day of therapy. Most importantly, no relationships were observed between concomitant medications and either toxicities or clinical response to therapy. We conclude that patients who are receiving concomitant medications should not systematically be excluded from phase I studies. [© 1999 Lippincott Williams & Wilkins.]

Key words: Concomitant medications, investigational agents, phase I studies.

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Introduction

The primary objectives of phase I clinical trials of a new anti-cancer agent are to determine a safe dose for further studies of therapeutic activity and to define the qualitative organ system toxicities associated with the compound.[1] In addition, pharmacokinetic studies are often performed and the patients are observed carefully for any signs of anti-tumor activity. Patients who participate in these trials must have a microscopically confirmed diagnosis of disseminated cancer which is no longer amenable to treatment with more established forms of therapy. As a consequence of these eligibility criteria, many patients have pre-existing comorbid conditions that require specific medications during the course of a phase I study. Most protocols ask that patients be taken off all but medically essential medications. However, as will be indicated below, many patients still receive a large number of concomitant medications. It is conceivable that some of these medications may alter the toxicities and/or the therapeutic activity of the investigational agent being studied; however, very few reports of phase I trials describe the concomitant medications that were administered to the patients or the relationships of these medications with other factors.

The characteristics of patients who participate in phase I studies are a consequence both of study-specific criteria and the selectivity of physicians.[2] These selection factors may affect the determination of the maximum tolerated dose (MTD) of drugs and under- or over-estimate the most appropriate dose for phase II studies. Many other factors may also have an impact on the MTD including age, underlying disease, performance status, number of prior anti-cancer therapies, number of metastatic sites, etc. The aim of

this project was to describe the concomitant medications received by patients who were selected for phase I studies and to determine their potential impact on results of these clinical trials. The specific objectives of this retrospective study were to document the number and types of concomitant medications that were administered on the first day of therapy to patients who participated in a large series of phase I clinical trials at a single institution, and to examine possible relationships between these medications and demographic characteristics, outcome measures and toxicities.

Table 1. Phase I clinical trials

Protocol	Drug	Open to accural	Courses			Recommended phase II dose
			N	Median	(Range)	
W82-716	Echinomycin	06/28/82	44	1	(1–10)	1600 $\mu g/m^2$ CI q 28 days with preRX antiemetics
W83-0089	Bisantrene/Mitoxantrone	03/01/83	11	2	(1–11)	recommended phase II dose not determined
W82-1515	Tiazofurin	03/04/83	20	1	(1–2)	1100 mg/m^2 q d × 5 q 28 days
W82-1404	2-Fluoro-ara-amp	03/05/83	13	2	(1–7)	18 mg/m^2 for patients with prior RX + XRT and 25 mg/m^2 with no prior RX
T83-1046	Menogaril	11/03/83	24	2	(1–10)	between 200 + 256 mg/m^2 i.v. q 28 days
T83-1302	2-Fluoro-ara-amp IP	05/31/84	6	1.5	(1–9)	recommended phase II dose not determined
T84-0351	Tiazofurin	08/23/84	12	2.5	(1–6)	1100 mg/m^2 intermittent weekly × 3 q 5 weeks
T84-0302	Didemnin B	12/11/84	45	1	(1–12)	2.67 mg/m^2 i.v. over 30 min q 28 days without prophylaxsis; antiemetics and 3.47 mg/m^2 if an antiemetic regimen is used
T85-0188	Nafidamide	11/06/85	38	1	(1–15)	918 mg/m^2 i.v. over 30–120 min q 28 days with dose escalation to myelotoxicity
T85-0244	Flavone acetic acid	03/14/86	38	1	(1–6)	8 mg/m^2 weekly × 4 q 5 weeks
T85-0200	Oral menogaril	03/17/86	12	2.5	(1–9)	not recommented for phase II evaluation
T85-0276	Dexoyspergualin	07/13/86	56	2	(1–14)	1800 mg/m^2 CI over 120 h q 28 days
T-86-0250	Trimetrexate for leukemia	01/16/87	7	1	(1–2)	9 mg/m^2 i.v. × 5 days q 21 days
T86-0277	Tumor necrosis factor	06/16/87	11	1	(1–6)	recommended phase II dose not determined
T87-0053	Taxol	06/19/87	31	2	(1–34)	225 mg/m^2 i.v. over 6 h q 21 days
T87-0315	Hepsulfam	02/16/89	29	2	(1–4)	150 mg/m^2 i.v. q 21–35 days
T88-0244	Liposomal doxorubicin	05/12/89	31	2	(1–7)	30 mg/m^2 i.v. weekly × 4 q 6 weeks
T89-0234	Ormaplatin	05/04/90	35	2	(1–5)	recommended phase II dose not determined
T89-0136	Acivicin with aminosyn	08/09/90	23	2	(1–6)	50 mg/m^2 day CI × 72 h q 6 weeks
T90-0101	Topotecan	10/12/90	45	3	(1–22)	0.87 mg/m^2 week CI × 5 days q 21 days; 1.6 mg/m^2 day × 3 d CI q 21 days
T90-0002	Terephthalamide	05/01/91	13	2	(1–4)	not recommended for phase II evaluation
T91-0155	2-Chlorodeoxyadenosine	04/01/92	23	2	(1–2)	6.5 mg/m^2/day CI × 5 days q 28 days
T92-0008	Topotecan/VP16	05/20/92	50	2	(1–11)	minimally preRx, 68 mg topotecan/m^2 day CI days 1–3 and 75 mg etoposide/m^2 days 7–9
T91-0118	Hydroxyurea i.v. versus oral	07/27/92	29	2	(1–6)	recommended phase II dose not determined
T93-0070	Topotecan	01/27/94	30	3	(1–21)	14 mg/m^2 orally q 3 weeks
T94-0143	BCNU + temozolomide	05/18/95[a]	8	1.5	(1–2)	ongoing trial
T94-0124	Rhizoxin	10/25/95[a]	3	2	(1–3)	ongoing trial
T94-0136	Rebeccamycin	11/10/95[a]	3	2	(1–4)	ongoing trial

[a]Still open to accrual.

Patients and methods

Phase I studies

Between 1982 and 1996, the University of Texas Health Science Center at San Antonio and the Cancer Therapy and Research Center conducted 28 phase I clinical trials of potential anti-cancer agents under agreements with the National Cancer Institute (Table 1). Twenty-five of these studies were completed at the time of this analysis and three remain open to accrual. These trials evaluated single investigational chemotherapeutic agents, single investigational cytokines, and combinations of investigational and conventional agents.

Patients

All patients (n=690) who were enrolled on the 28 phase I clinical trials listed in Table 1 between 28 June 1982 and 4 January 1996, and who were off-study at the time of analysis were included in this study. For each patient, the number and type of concomitant medications that were administered on the first day of therapy (course 1, day 1) were retrieved from the database, along with gender, age, cancer diagnosis, performance status, prior therapy (surgery, radiotherapy, chemotherapy, endocrine therapy, immunotherapy), dose of the investigational agent received during the first course of therapy, number of courses received, maximum toxicity while on-study duration on-study and overall best response.

Concomitant medications were grouped into 31 categories based on the American Hospital Formulary Service 1993, American Society of Hospital Pharmacists.[3] Indications for the various concomitant medications were grouped into 19 categories and the cancer diagnosis was grouped into 13 classes according to the site of disease. Performance status was rated according to the SWOG system and toxicities were graded using the NCI Common Toxicity Criteria.[4]

Patient characteristics are shown in Table 2. The majority of the patients were men (67%) and the median age was 60 (range 19–88). Performance status at enrollment was 2 or better for 95% of the patients. Nearly all patients had solid tumors (30.4% had a digestive carcinoma and 28.6% a lung cancer), but eight (1.2%) had hematological malignancies. All but four patients had received some form of prior therapy (surgery, 86.5%; chemotherapy, 82.5%; radiotherapy, 52.6%; hormone therapy, 6.7%; immunotherapy, 5.9%).

Toxicities and administration of concomitant medications might be related to the dose of the experimental agent that the patient received. Since many different agents were evaluated in these studies, we converted the dose received by each patient during the first course of therapy into a percentage of the recommended phase II dose that was eventually

Table 2. Patient characteristcs

Men/women	482/208
Median age [years (range)]	60 (19–88)
Performance status	
0	169 (24.5%)
1	350 (50.7%)
2	135 (19.6%)
3	35 (5.1%)
4	1 (0.1%)
Prior treatment	
surgery	597 (86.5%)
chemotherapy	569 (82.5%)
radiotherapy	363 (52.6%)
chemotherapy and radiotherapy	317 (45.9%)
hormone therapy	46 (6.7%)
immunotherapy	41 (5.9%)
Tumor types	
digestive	210 (30.4%)
colorectal	171
pancreas	16
stomach	10
hepatocellular	7
bile duct/gall bladder	4
small bowel/appendix	2
lung	197 (28.6%)
kidney	51 (7.4%)
head and neck	37 (5.4%)
breast	30 (4.3%)
sarcoma	28 (4.1%)
ovary	27 (3.9%)
bone	15 (2.2%)
prostate	18 (2.6%)
uterus	12 (1.7%)
skin	13 (1.9%)
hematologic malignancies	8 (1.2%)
others	44 (6.4%)
No. of courses received (median, range)	2 (1–34)
Days on-study (median, range)	49 (1–776)
Percent of recommended phase II dose received	83 (2–250)
Maximum toxicity	
none	59 (8.6%)
grade 1	188 (27.2%)
grade 2	205 (29.6%)
grade 3	144 (20.9%)
grade 4	91 (13.2%)
grade 5 (fatal)	3 (0.4%)
Best response	
complete response	3 (0.4%)
partial response	9 (1.3%)
minor response	14 (2.0%)
stable disease	289 (41.9%)
progressive disease	307 (44.5%)
not applicable	68 (9.9%)

determined for each study (Table 1). The recommended phase II dose was not determined for six studies and three studies were still open at the time of this review. Therefore, the dose percentage could not be computed for the 120 patients treated on these nine studies (32% of all patients).

Statistical analyses

The primary variables of interest were the administration of various concomitant medications on day 1 of therapy. Non-parametric Spearman rank correlation coefficients were used to evaluate the relationships between the number of concomitant medications administered and other continuous factors (e.g. age, performance status, maximum grade of toxicity, duration of time on-study, number of courses of therapy received and dose received). For each of the 31 classes of medications, every patient was assigned a value of 0 or 1 depending on whether or not the patient received an agent in that class on the first day of therapy. Relationships between each class and other factors that were expressed as dichotomous variables (e.g. gender, prior therapy, treatment response, coded performance status, and toxicity grade) were examined using χ^2 tests and Fisher's exact tests, and relationships with continuous variables were tested by Wilcoxon rank-sum tests. All tests were two-sided and were performed at the 1% level of significance.

Results

The 690 patients included in this study participated in 28 phase I clinical trials from 1982 to 1996 and received a total of 1650 cycles of treatment. The median number of cycles of treatment per patient was 2 (range 1-34) and the median duration on-study was 49 days (range 1-776). During the 15 year study period, patients received more courses and were on-study longer as time passed. The median duration on study was 36 days during 1982-1986, 45 days during 1987-1991 and 56 days during 1992-1996.

For the 570 patients for whom dose received during the first course of therapy as a percentage of the recommended phase II dose could be computed, the median dose received was 83% (range 2-250%). There were no correlations between the dose received during the first course of therapy and either the number of courses (r=0.07) or the duration on-study (r=−0.05).

Only 8.6% of patients experienced no toxicity while on-study, while 27.2, 29.6, 20.9 and 13.2% had maximum toxicity grades during the study of 1, 2, 3 and 4, respectively. Only three toxic deaths occurred among the 690 patients (0.4%). The toxicity grade was directly associated with the dose received (r=0.26; $p<0.0001$), but was unrelated to the number of courses received (r=0.04) or to the duration on-study (r=0.05).

No treatment responses were observed in 86.4% of the patients (44.5% had progressive disease and 41.9% had stable disease) and 3.8% had complete, partial or minor response to therapy. Approximately 10% of patients were not evaluable for response. The number of responses was too small to perform definitive analyses, but there were no apparent relationships between clinical response and maximum toxicity or dose received. Responding patients did receive more courses of therapy and were on-study longer ($p<0.0001$).

Concomitant medications

All but 63 patients received at least one concomitant medication on the first day of study (90.9%). The median number of medications was 4 (range 0-22). There was a significant decrease in the number of medications during the past 5 years (median 2, compared to medians of 4 for 1982-1986 and 1986-1991; $p<0.0001$). The frequency of each class of medication is displayed in Table 3. The most frequent classes of medications administered were: analgesics and antipyretics (66%), psychotherapeutic agents (47%), laxatives (33%), antiemetics (29%), antihistamines (25%), antacids (23%), and corticoids (14%). Five classes of medications were never administered: blood derivatives, cholinergics, adrenergic blockers, coagulants and hemostatics, and general anesthetics.

Relationships with gender

The number of concomitant medications on day 1 did not differ by gender (males: median 4, range 0-17; females: median 4, range 0-22; p=0.90). However, hormones and antiemetics were more frequently administered to females than to males, $p<0.0001$ and p=0.006, respectively.

Relationships with age

The number of concomitant medications was not related to the age of the patient, but administration of certain medications was associated with age. Cardiovascular agents (p=0.0008), eye, ear, nose, throat

Table 3. Concomitant medications—classification, frequency and associations

At least one medication	91%	poor PS (p=0.02), shorter study duration (p<0.0001)
Analgesics/antipyretics	66%	poor PS (p<0.0001), more prior XRT (p<0.0001), shorter study duration (p=0.0001), younger age (p=0.0001), fewer digestive tumors (p=0.009)
Psychotherapeutic	47%	poor PS (p=0.002), decreased toxicity grade (p=0.006)
Laxatives	33%	poor PS (p<0.0001)
Antiemetics	29%	females (p=0.006)
Antihistamines	25%	no significant associations
Antacids/absorbents	23%	less prior chemotherapy (p=0.004), shorter study duration (p=0.003)
Corticoids	14%	more prior XRT (p=0.0002), shorter study duration (p=0.0001)
Cardiovascular	13%	less prior chemotherapy (p=0.002), older age (p=0.0008)
Anti-infectives	10%	no significant associations
Hormones	12%	females (p<0.0001)
Miscellaneous	12%	poor PS (p=0.007), more dose received (p=0.0002)
Ionic regulation	11%	increased toxicity grade (p=0.0004)
Adrenergics	8%	lung cancer (p=0.001), more prior XRT (p=0.007)
Diuretics	7%	no significant associations
Smooth muscle relaxants	7%	poor PS (p=0.001), lung cancer (p=0.001), older age (p=0.005), shorter study duration (p=0.009)
Vitamins	7%	no significant associations
Eye, ear, nose, throat	4%	older age (p=0.002)
Hypotensive agents	4%	less prior chemotherapy (p=0.004)
Anticoagulants	3%	no significant associations
Antitussives	3%	no significant associations
Skin, mucous	3%	no significant associations
Anticonvulsants	3%	younger age (p=0.007), more prior XRT (p=0.0003)
Antidiarrheals	2%	no significant associations
Anticholinergics	2%	no significant associations
Local anesthetics	0.3%	no significant associations
Hematopoietic GF	0.2%	no significant associations
Blood derivatives	0	no significant associations
Cholinergics	0	no significant associations
Adrenergics blockers	0	no significant associations
Coagulants–hemostatics	0	no significant associations
General anesthetics	0	no significant associations

PS, performance status; XRT, radiation therapy; GF, growth factor.

preparations (p=0.002) and smooth muscle relaxants (p=0.005) were more frequently taken by older patients. Analgesics/antipyretics (p=0.0001) and anticonvulsants (p=0.007) were more frequently administered to younger patients.

Relationships with tumor type

The number of concomitant medications was not significantly different among tumor types, but significant relationships were observed for specific classes of agents and indications. Due to a relatively small number of patients with some tumor types, we considered only three groups: tumors of the digestive system (n=210), lung cancer (n=197) and all other cancers (n=283). Lung cancer patients received significantly more adrenergics (p=0.001) and smooth muscle relaxants (p=0.001), compared to patients with other types of cancer. Compared to other patients, those with tumors of the digestive system were less likely to receive analgesics/antipyretic (p=0.009).

Relationships with prior therapy

The number of concomitant medications did not correlate with prior surgery, prior radiation therapy, prior chemotherapy, prior endocrine therapy or prior immunotherapy. No associations were observed between administration of any of the classes of concomitant medications and prior surgery, prior endocrine therapy or prior immunotherapy. However, patients who received prior radiotherapy were more likely to be

administered analgesics/antipyretics ($p<0.0001$), corticoids ($p=0.0002$), anticonvulsants ($p=0.0003$) and adrenergics ($p=0.007$). Patients who had not received prior chemotherapy were more likely to receive cardiovascular agents ($p=0.002$), hypotensive agents ($p=0.004$) and antacids/absorbents ($p=0.004$).

Relationships with performance status

The total number of concomitant medications administered on day 1 was directly related to performance status ($r=0.27$; $p<0.0001$). When patients were classified as having poor performance status (2-4) or good performance status (0-1), 95% of poor performance status patients received concomitant medications, compared to 89% of good performance status patients ($p=0.02$). The classes of agents that were statistically associated with poor performance status patients were: laxatives ($p<0.0001$), analgesics/antipyretics ($p<0.0001$), smooth muscle relaxants ($p=0.001$), psychotherapeutic ($p=0.002$) and miscellaneous ($p=0.007$).

Relationships with study duration

The number of concomitant medications on day 1 was inversely related to the number of courses of therapy received ($r=-0.15$) and the duration on-study ($r=-0.18$) ($p<0.0001$ for each factor). Patients who received analgesics/antipyretics ($p=0.0001$), corticoids ($p=0.0001$), antacids/absorbents ($p=0.003$) or smooth muscle relaxants ($p=0.009$) remained on study for less time than patients who did not receive these agents.

Relationships with dose received

The number of concomitant medications received was not related to the dose of the investigational agent ($r=0.002$). The mean percentage of the recommended phase II doses was 82% regardless of whether patients received concomitant medications or not ($p=0.086$). Miscellaneous agents was the only class with a statistically significant relationship to dose ($p=0.0002$). Subset analyses within this class did not reveal any clinically significant findings.

Relationships with toxicities

No relationship was observed between the total number of medications received and the maximum toxicity grade ($r=0.05$). Patients were then classified as having high grade toxicity during their courses of therapy if the maximum toxicity grade was 3, 4 or 5. The percentage of patients with high grade toxicities was nearly the same for patients who received concomitant medications (35%), compared to those who did not receive medications (32%) ($p=0.68$). Of interest, however, administration of ionic regulation agents was significantly associated with high grade toxicity ($p=0.0004$) and patients who received psychotherapeutic agents had less high grade toxicity ($p=0.006$).

Relationships with response to therapy

Only 3.8% of patients had complete, partial or minor response to therapy, so relationships with administration of concomitant medications would be very difficult to detect. However, the proportion of patients who responded to therapy was nearly the same whether they received concomitant medications (3.7%) or not (4.8%) ($p=0.72$). No significant relationships were observed between clinical response and specific classes of agents or indications for their use.

Discussion

The incidence of concomitant medications administered to patients participating in phase I clinical trials of anti-cancer agents is very high. Among 690 patients enrolled on 28 studies, 90.9% received at least one medication on the first day of therapy. The number of concomitant medications was also important, since patients received a median of four concomitant medications (range 0-22) at study entry. More than 60% of patients received medications for pain, 43% for depression/anxiety/mood modification, 34% for nausea/vomiting and 34% for constipation.

Several classes of agents were associated with pre-existing conditions such as decreased performance status, age of the patient, tumor type and prior anti-cancer therapy received. Correlations were also found between administration of concomitant medications and subsequent events, including duration of time on-study and maximum toxicity experienced during the study. However, no relationships were observed between these medications and the amount of the investigational agent received or response to the anti-cancer agents being evaluated in these phase I clinical trials.

Caution must be taken when interpreting the statistically significant relationships observed in this

retrospective analysis. Since a large number of comparisons were made (~600), some results will be statistically significant by chance alone. We elected to perform all tests at the 1% level of significance to partially correct for the multitude of comparisons, but we still expect that approximately six significant results may be due to chance.

Nevertheless, several observations are supported by clinical evidence. One expects that patients who received medications for pain and other debilitating conditions would have decreased performance status, and that this might translate into a shorter duration on-study. It is also unsurprising that patients with lung cancer tended to have pre-existing pulmonary disorders and infections. Patients with CNS conditions received more prior radiotherapy, while patients with prior cardiovascular problems had received less chemotherapy and radiotherapy. The relationship between age and some classes of concomitant medications should be investigated further. It might be preferable to design specific phase I studies for older patients who are either excluded from phase I studies or are treated with doses that were determined for younger patients.

The relationships between certain classes of medications and the maximum grade of toxicity are interesting and might be used to generate testable hypotheses for future studies. However, such hypotheses must take into account the dose and dose level of the anti-cancer agent received by the patient. Since, by definition, phase I trials involve dose escalation from a relatively non-toxic dose to the MTD, the majority of patients on phase I studies will not receive the maximum dose and may not experience as many severe toxicities as patients on subsequent phase II studies. However, patients who receive ionic regulation agents may have physiologic disorders which require supportive care, which might explain the relationships with high toxicity grade. On the other hand, patients receiving psychotherapeutic agents have less severe toxicity. This may reflect pharmacologic interactions between psychotherapeutic agents and some anti-cancer drugs.

The patients who participated in these studies were highly selected for good performance status. Perhaps a good performance status is more important than the presence of concomitant medications on the first day of study for a successful phase I clinical trial. The absence of a relationship between concomitant medications and dose received during the first course of therapy, despite the inverse relation with duration of time on study, is of particular importance since toxicities define the MTD which is the principal objective of all phase I studies. The lack of correlation between response to the anti-cancer agent and administration of concomitant medications, while not definitive due to small numbers, is comforting. This suggests that there is no obviously negative impact of concomitant medications on the efficacy of the agents being evaluated in these phase I trials. An obvious question is whether any of the concomitant medications alter the pharmacokinetic or pharmacodynamic profiles of investigational agents that were studied in these clinical trials. Given the wide range of concomitant medications and the relatively small numbers of patients on each trial, it was impossible to address this question in this study.

Conclusion

While these results are generalizations based on data from 28 different phase I studies and may differ for specific agents, patients who are receiving concomitant medications should not be systematically excluded from participation in phase I trials of potential anti-cancer agents.

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