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Selective kinase inhibition with daily imatinib intensifies toxicity of chemotherapy in patients with solid tumours

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ABSTRACT

The aim of this study was to determine the safety and maximum-tolerated doses of imatinib combined with cytotoxic chemotherapy (either gemcitabine or doxorubicin). Patients with advanced solid tumours were enrolled separately in two different combinations of imatinib with chemotherapy (imatinib + gemcitabine *or* imatinib + doxorubicin). A standard modified Fibonacci inter-cohort dose escalation was planned for each combination. Sixteen patients were accrued. Seven patients received gemcitabine and imatinib. A separate cohort of nine patients received imatinib and doxorubicin. In both groups, dose-limiting toxicity (DLT) was observed at the initial dose level requiring dose reductions for subsequent cohorts. Further DLTs were observed necessitating closure of the protocol. Daily dosing of imatinib with concurrent administration of cytotoxic chemotherapy (either gemcitabine or doxorubicin) at standard doses was associated with toxicity that was clinically unacceptable. It remains unclear whether addition of growth factors might improve tolerability for imatininb in combination with cytotoxic chemotherapy.

1. Introduction

Despite the development of newer molecular targeted approaches to cancer therapy, cytotoxic chemotherapy remains a major modality for treatment of patients with common solid tumours. Emergence of resistance to these drugs remains a common problem and limits the effectiveness of chemotherapy. A number of mechanisms underlying chemoresistance have been proposed, including the development of genetic mutations preventing chemotherapy-induced apoptosis, or the high interstitial pressures that exist within the tumour matrix,[1] resulting in suboptimal drug delivery to cancer cells resident within large tumours. The molecular mechanisms underlying changes in interstitial pressures are dependent on a number of influences. Signalling through the platelet-derived growth factor (PDGF) receptor and ligand system is believed to play a central role in modulating intratumoural interstitial fluid pressures, particularly via the PDGFβ receptor.[2–4]

Deregulation of PDGF-receptor signalling has also been implicated in several types of cancers including prostate,[5,6] lung,[7] breast,[8] sarcomas,[9] gliomas,[10–12] and ovarian cancers.[13]

Imatinib mesylate (Glivec®, also known as Gleevec™ in North America; Novartis Pharmaceuticals) is a small molecule phenylaminopyrimidine derivative that selectively inhibits a number of protein tyrosine kinases involved in cellular

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proliferation. These include c-Abl, Bcr-Abl, ARG (Abl-related tyrosine kinase), the platelet-derived growth factor receptor (PDGF-R), and KIT, the receptor for Stem Cell Factor.[14–16] The clinical utility of imatinib has been clearly established in chronic myeloid leukaemia (CML) and advanced gastrointestinal stromal tumour (GIST) due to the inhibition of the oncogenic Bcr-Abl, KIT, and/or PDGFR-alpha kinases, respectively.[17–21]

Imatinib has shown promising efficacy in a number of diseases with known deregulation of PDGFR kinase activity, including dermatofibrosarcoma protuberans,[22–24] hypereosinophilic syndrome,[25] and chronic myelomonocytic leukaemia.[26–28]

Preclinical models testing the combination of imatinib with cytotoxic chemotherapy have suggested there might be synergy between these mechanistically distinct therapeutic strategies. Imatinib plus cytarabine or daunorubicin led to increased apoptosis in Bcr-Abl-positive human leukaemia cell lines through down-regulation of anti-apoptotic signalling.[29,30] Synergistic effects have also been seen when combining imatinib with paclitaxel in mouse models of prostate cancer[6] and ovarian cancer;[13] and when combining imatinib with gemcitabine in a mouse model of pancreatic cancer.[31] In addition, an in vitro model using rat colon carcinoma demonstrated decreased interstitial fluid pressure (IFP) in response to imatinib,[3] and was seen in tumour models in mice treated with imatinib and concurrent chemotherapy.[4] These changes in IFP are likely due to inhibition of PDGFβ signalling that is up-regulated in the tumour vasculature and desmoplastic stromal cells in the tumour microenvironment. By decreasing this abnormally high IFP, it is possible that increased transport would be allowed from the tumour capillaries to the interstitium. This, in turn, could be associated with improvement in delivery of cytotoxic chemotherapy to the tumour cells. This has been suggested as a novel way to improve effective drug delivery into the complex microenvironment of solid tumours. Besides these potential effects on the tumour microenvironment, the combination of imatinib with cytotoxic chemotherapy might also lead to increased cytotoxicity through direct effects via inhibition of anti-apoptotic signalling in the tumour cells, perhaps acting through PDGF receptors directly.

In order to test these hypotheses, we began studies to assess the safety of two separate combinations of imatinib with conventional chemotherapeutic drugs (either in combination with gemcitabine or with doxorubicin). Separate cohorts of patients were enrolled into dose escalation trials to determine the safety and tolerability profiles, the maximum-tolerated doses, and any dose-limiting toxicities of the combination of imatinib with these two widely used cytotoxic agents.

2. Patients and methods

2.1. *Eligibility*

The following eligibility criteria were required: patients with solid tumour malignancies for which there were no standard effective therapies; Eastern Cooperative Oncology Group performance status 0–2; estimated life expectancy of at least 3 months; no prior radiation therapy or systemic cancer therapy within 4 months; no major surgery within 2 weeks; full recovery from any toxic effects of prior treatments; no other active primary malignancy; no other severe and/or life-threatening medical condition including, symptomatic congestive cardiac failure within 6 months of study entry , acute or chronic liver disease or HIV infection; absence of pregnancy or lactation and willingness to use contraception. The Dana-Farber/Harvard Cancer Center institutional review board approved this investigation. All patients gave written informed consent prior to study entry as per federal and institutional guidelines.

Patients were required to have adequate end-organ function.

Specific eligibility criteria for the doxorubicin and imatinib combination included a lifetime cumulative doxorubicin dose of <300 mg/m^2; absence of prior cardiac irradiation; left ventricular ejection fraction within normal limits.

In the study of each combination, the study rules were amended after the first dose cohort was treated to exclude patients who had received more than one prior chemotherapy regimen, or who had received prior pelvic irradiation (see Section 3 for further detail about the toxicities that led to this amendment).

2.2. *Study design, dosage and drug administration*

The study was supported in part by funds and with drug supply provided by Novartis Pharmaceuticals. The study was designed and conducted by the investigative team, and all data was held by the investigators. Imatinib mesylate was supplied as 100 mg capsules by Novartis. Gemcitabine and doxorubicin were obtained commercially.

Patients received drug administration according to the schedule outlined in Tables 1 and 2. Patients were instructed to take imatinib at the same time every day, with a full glass of water and along with food. Gemcitabine was administered

Table 1 – Treatment schedule for gemcitabine and imatinib

Dose level	Imatinib mesylate (mg/day)	Gemcitabine
−1	300	700 mg/m^2 IV days 1 and 8/ every 21 days
0	400	700 mg/m^2 IV days 1, 8 and 15/ every 28 days
1	400	800 mg/m^2 IV days 1, 8 and 15/ every 28 days

Table 2 – Treatment schedule for doxorubicin and imatinib

Dose level	Imatinib mesylate (mg/day)	Doxorubicin
−1	300	50 mg/m^2 IV day 1/every 21 days
0	400	50 mg/m^2 IV day 1/every 21 days
1	400	60 mg/m^2 IV day 1/every 21 days

intravenously over 30 min via an electronic infusion pump. Doxorubicin was administered as an intravenous bolus.

2.3. Study design and rules for dose escalation or dose de-escalation

Dose assignments were based on the modified Fibonacci three-per-cohort Phase I study design. Enrollment began at dose level 1 (see Tables 1 and 2). Intrapatient dose escalations were not allowed. For enrollment to proceed beyond the first dose level, patients were required to be treated for 1 cycle, and have all safety data reviewed. If no dose-limiting toxicity (DLT) was seen, then enrollment would be allowed to continue with increase to the next dose level for the subsequent cohort. If two or more DLTs were seen in the first 3 patients, then enrollment was to continue at a reduced dose level (denoted as dose level –1), with maximum subsequent increase in subsequent cohorts to dose level 0. If 1 DLT was seen, 3 additional patients were to be enrolled at that dose level; and if no further DLT was seen (i.e., total of 1 DLT per 6 patients) then enrollment was to continue to the next dose level. If further DLTs were seen (i.e., total $\geqslant$2 DLTs per 6 patients), then the previous dose level would be considered the maximum tolerated dose (MTD). Once MTD was determined, the study was designed to enroll approximately an additional 10 patients at the MTD level.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. For both studies, DLT was defined as any grade 3 or 4 non-haematologic toxicity or any clinically relevant grade 3 or 4 haematologic toxicity (defined as ANC $<1.0\times10^9$/l persisting for >7 days, an episode of fever >38.5° Celsius with neutropenia, grade 4 anaemia, or grade 4 thrombocytopenia).

For the gemcitabine and imatinib combination, further criteria defining a DLT included an ANC of $<1.5\times10^9$/l on day 8 or day 15 (only for dose level 1) of cycle 1 leading to a delay in administering gemcitabine dosing beyond day 15 or a platelet count of $<50\times10^9$ on day 8 or day 15 of cycle 1 leading to a delay in chemotherapy.

For doxorubicin and imatinib, further criteria defining a DLT included an ANC of $<1.5\times10^9$/l on day 1 of cycle 2 leading to a delay of planned doxorubicin dosing; any grade of bilirubin toxicity on day 1 of cycle 2; clinically apparent congestive cardiac failure or a reduction in LVEF below the institutional lower limit of normal (50%) or a fall in LVEF of >15% in a patient whose baseline LVEF was >65%.

The prophylactic use of growth factors was not permitted. However, therapeutic use of haematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) was permitted per the clinical practice guidelines of the American Society of Clinical Oncology.

For either combination, patients were eligible to receive continued cycles of drug administration if they were clinically well, recovered from all toxicities and had no evidence of progressive disease (PD). Treatment was discontinued if chemotherapy was delayed for >14 days due to toxicity, or if patients developed a grade 3 or higher non-haematologic toxicity after a dose reduction. Patients who experienced a grade 3 or higher non-haematologic toxicity for cycle 2 and beyond recommenced drug once toxicity resolved to grade 1 or less; with a 25% reduction in the dose of chemotherapy, but no adjustment in imatinib dose. For doxorubicin and imatinib, treatment with doxorubicin ceased once the cumulative lifetime doxorubicin dose reached 480 mg/m^2. Following recognition of haematologic toxicities with subsequent study amendment, patients who developed severe neutropenia (neutrophil count of $\leqslant1.0\times10^9$/l) were instructed to hold any further imatinib dosing until ANC recovered to $>1.0\times10^9$/l.

2.4. Pretreatment and follow-up studies

A history and physical examination as well as laboratory studies were performed at baseline to determine eligibility. Measurable disease, if present, was documented by means of appropriate imaging studies. Imaging studies were to be repeated after every 2 cycles of treatment. Objective measurement of tumour mass was assessed in accordance with Response Evaluation Criteria in Sold Tumours (RECIST).[32]

For gemcitabine and imatinib, complete blood counts were repeated on days 1, 8 and 15, while serum chemistries were performed on days 1 and 15 of each cycle. Patients had a physical examination on day 1 and 8 of each cycle.

For doxorubicin and imatinib, complete blood counts were repeated on days 1, 8, 11 and 15 of cycle 1, and then on days 1, 8 and 15 of subsequent cycles. Serum chemistries were performed on days 1 and 15 of each cycle. Patients had a physical examination on each day 1. Cardiac assessment included a baseline EKG, and a MUGA scan. MUGA scans were repeated after every 2 cycles, or after every cycle if the patient had reached a lifetime cumulative dose of doxorubicin exceeding 400 mg/m^2.

3. Results

3.1. General

Seven patients were enrolled, in total, to receive gemcitabine and imatinib. Nine patients were enrolled to receive doxorubicin and imatinib. Baseline characteristics and treatment outcomes for each group are listed in Tables 3 and 4.

3.2. Safety, tolerability, and dose-limiting toxicities

Myelosuppression was the principal DLT observed in both combination studies. For gemcitabine and imatinib, 7 patients were treated for a total of 7 cycles. As outlined in Table 5, 2 of the first 3 patients treated on the initial cohort (dose level 1) developed significant neutropenia. Patient 1 had a neutrophil count of 1.08×10^9 on cycle 1, day 15, which was below that required for treatment with gemcitabine (1.5×10^9); this defined the DLT. Patient number 3 developed grade 3 neutropenia, with a neutrophil count of 0.78×10^9 on cycle 1, day 8; this constituted another DLT at this dose and schedule. Patient number 4, who was treated on dose level −1, developed grade 3 thrombocytopenia on cycle 1, day 15 (nadir platelet count of 26×10^9). Patient number 7 experienced the second DLT on dose level −1, with the development of grade 3 fatigue on cycle 1 day 21, and this led to termination of the study.

For doxorubicin and imatinib (Table 6), the first 2 patients treated on dose level 1 developed DLTs. Patient number 1,

Table 3 – Summary of patient characteristics and outcome: gemcitabine and imatinib

Patient number	Dose level	Age/sex	ECOG	Disease type	No. of prior therapies	No. of cycles received	Best response	Reason for removal
1	1	M/31	0	Desmoid tumour	2	1	Unknown	DLT
2	1	M/38	2	Neuroendocrine carcinoma	2	1	PD	PD
3	1	M/71	0	Metastatic angiosarcoma	4 + RT	1	Unknown	DLT
4	−1	F/30	2	Adrenocortical carcinoma	1	1	PD	DLT
5	–	F/56	0	Leiomyosarcoma	1	1	Unknown	Severe depression
6	–	F/49	0	Adrenocortical carcinoma	1	1	PD	PD
7	–	M/63	1	Non-small cell lung carcinoma	1 + RT	1	Unknown	DLT

PD: progressive disease; DLT: dose-limiting toxicity; RT: radiotherapy.

Table 4 – Summary of patient characteristics and outcome: doxorubicin and imatinib

Patient number	Dose level	Age/sex	ECOG	Disease type	No. of prior therapies	No. of cycles received	Best response	Reason for removal
1	1	M/48	1	Poorly differentiated carcinoma	0	1	Unknown	DLT
2	1	F/60	1	Adenocarcinoma – pancreas	3	1	PD	DLT
3	−1	F/53	0	Leiomyosarcoma	0	10	PR	DLT
4	−1	F/53	1	Adenoid cystic carcinoma	1 + RT	1	Unknown	DLT
5	−1	M/64	0	Leiomyosarcoma	0	2	PD	PD
6	−1	F/55	0	Leiomyosarcoma	1	2	PD	PD
7	−1	F/71	0	Metastatic angiosarcoma	0	2	PD	PD
8	−1	F/61	0	Leiomyosarcoma	0	2	PD	PD
9	−1	M/55	1	Adenocarcinoma – gastric	0	2	PD	PD

PD: progressive disease; DLT: dose-limiting toxicity; RT: radiotherapy; PR: poor response.

Table 5 – Dose-limiting toxicities: gemcitabine and imatinib

Patient number	Type of DLT	Dose level	Cycle number	Previous treatment
1	Grade 2 neutropenia resulting in treatment delay	1	C1D15	Liposomal doxorubicin, vinorelbine
3	Grade 3 neutropenia	1	C1D8	Paclitaxel, liposomal doxorubicin, vinorelbine, endostatin, radiotherapy to scalp
4	Grade 3 thrombocytopenia	−1	C1D15	Adriamycin/cisplatin/etoposide
7	Grade 3 fatigue	−1	C1D22	Carboplatin/paclitaxel, radiotherapy-whole brain

Table 6 – Dose-limiting toxicities: doxorubicin and imatinib

Patient number	Type of DLT	Dose level	Cycle number	Previous treatment
1	Grade 3 neutropenia	1	C1D15	None
2	Grade 3 nausea and vomiting	1	C1D4	Gemcitabine, raf-kinase inhibitor, capecitabine
3	Grade 2 cardiac-left ventricular function	−1	Cycle 9	None
4	Grade 3 neutropenia	−1	C1D15	Cyclophosphamide/methotrexate/5-fluorouracil, radiotherapy to breast and neck

developed grade 3 neutropenia on cycle 1, day 15, with a nadir neutrophil count of 0.95×10^9. Patient number 2 developed grade 3 nausea and vomiting despite anti-emetics. Patient number 3, the first patient treated on dose level −1, had no history of heart disease. She tolerated treatment well for nine cycles of combination drug administration but then developed an asymptomatic reduction in LVEF (from 60% to 40%). This event was considered a DLT, and the patient's treatment was stopped. The patient was managed with beta blockade and ACE inhibition. Follow-up cardiac assessment 6 months later

Table 7 – All treatment-related toxicities, listed by grade

	Gemcitabine and imatinib						Doxorubicin and imatinib					
	Dose level						Dose level					
	1			−1			1			−1		
No. of patients	3			4			2			7		
Total no. of cycles	3			4			2			21		
Toxicity and grade	1	2	3	1	2	3	1	2	3	1	2	3
Hemoglobin	–	–	–	–	–	–	–	–	–	1	1	–
Neutrophils	1	1[a]	1[a]	–	1	–	–	–	1[a]	–	–	4[a]
Platelets	–	1	–	–	–	1[a]	1	–	–	–	–	–
Edema	–	–	–	–	–	–	–	–	–	1	–	–
Fatigue	1	–	–	–	–	1[a]	–	1	–	–	3	–
Nausea	1	–	–	2	–	–	1	–	1[a]	4	1	–
Vomiting	–	–	–	1	–	–	–	–	1[a]	1	1	–
Diarrhoea	–	–	–	–	–	–	–	–	–	3	–	–
Anorexia	–	–	–	–	1	0	–	–	–	2	–	–
Cardiac–LVF	–	–	–	–	–	–	–	–	–	–	1[a]	–

Notes: Toxicities are as per Common Toxicity Criteria Grades, version 2.0.
a Patients who experienced dose-limiting toxicity (please note, nausea and vomiting occurred concurrently in the same patient and therefore reflect a singe DLT). Cardiac-LVF refers to cardiac left ventricular function.

revealed recovery of her LVEF to 64%. She remains alive and without cardiac symptoms. Patient number 4 developed grade 3 neutropenia on cycle 1, day 15 of treatment, with a nadir neutrophil count of 0.68×10^9, representing another DLT.

Importantly, no patient experienced infection or bleeding.

3.3. *Other toxicities*

A complete list of treatment related toxicities is provided in Table 7. Myelosuppression, in particular neutropenia, was the most common toxicity. Thrombocytopenia occurred in one patient, and was dose-limiting, as detailed above. Anaemia was less common, and may have reflected the short time on treatment by the majority of patients. Fatigue and nausea were the most common non-haematologic toxicities encountered. Nausea was typically associated with chemotherapy administration, and was more common in patients receiving doxorubicin and imatinib. It was usually mild in intensity and controlled with standard anti-emetics. Diarrhoea and edema, toxicities that are typically seen with imatinib administration, were not commonly seen, and again may have reflected the short duration of treatment. Patient 5 (see Table 3), who received the combination of gemcitabine and imatinib, developed severe depression on cycle 1 day 8. This was thought not to be related to treatment. However, it was considered to be in the best medical interest of the patient to discontinue protocol participation, rendering her ineligible for further assessment of response or toxicity. No other significant toxicities were noted with either combination regimen.

3.4. *Antitumour response*

Only 2 patients treated with the combination of gemcitabine and imatinib, and only 6 patients treated with doxorubicin and imatinib, were assessable for response (see Tables 3 and 4). Both evaluable patients on gemcitabine and imatinib developed progressive disease after 1 cycle of treatment. Of the 6 patients evaluable for response on doxorubicin and imatinib, 5 developed progressive disease after a maximum of 2 cycles of treatment. The only patient who achieved an objective response was patient 3, a 53-year-old woman with metastatic leiomyosarcoma, treated on dose level −1 with doxorubicin and imatinib. She had not received any previous systemic treatment for her disease. After 4 cycles of treatment, she had a confirmed partial response that was sustained until removal from study after cycle 9 was necessitated with the development of the asymptomatic drop in LVEF which was considered a cardiac DLT, as noted above.

4. Discussion

We set out to test two combinations of imatinib with cytotoxic chemotherapy in order to determine the safety, tolerability, maximum-tolerated doses, and any dose-limiting toxicities of the combination of daily oral administration of imatinib with either of two widely used cytotoxic agents, gemcitabine or doxorubicin. These combination regimens, however, demonstrated unacceptable toxicities in the schedule and doses employed without haematopoietic growth factor support resulting in termination of both studies after only a small number of patients were treated.

The predominant dose-limiting toxicity with either combination was myelosuppression, at a rate that was higher than would be expected if either of these drugs were administered as a single agent. In patients with solid tumours treated with imatinib as a single agent, at doses ranging from 400 to 800 mg/day, the incidence of grade 3 or 4 neutropenia is approximately 5%, and grade 3 or 4 thrombocytopenia <2%.[20,21,33] Rates of grade 3 or 4 neutropenia or thrombocytopenia seen with doxorubicin at similar or slightly higher doses to those used in this study are reported to be in the range of 10–20%.[34,35] Gemcitabine, when used as a single agent, is even less myelotoxic, with neutropenia or thrombocytopenia reported in up to 10% of patients.[36–38]

There are a number of possible explanations for the high incidence of unacceptable toxicity that was observed with these regimens. Pharmacokinetic profiles were not performed, as a direct pharmacokinetic interaction was not expected since these drugs are not metabolized via a common pathway. However, it remains theoretically possible that there may have been an unforeseen pharmacokinetic interaction.

Since imatinib is known to affect interstitial fluid pressures through inhibition of the PDGFR pathways, it is possible that the functional marrow or tissue concentrations of cytotoxic drugs may have been increased significantly, thereby leading to increased toxicities. Similar mechanisms of toxicity have been seen when inhibitors of multidrug resistance proteins were added to cytotoxic chemotherapies in an attempt to improve tissue drug delivery.[39–41]

There has been relatively limited published clinical experience evaluating combinations of imatinib and cytotoxic chemotherapy in patients with solid tumours. In a study evaluating imatinib in combination with docetaxel in patients with androgen-independent prostate cancer noted that >50% of patients treated at the MTD experienced a DLT. Interestingly, very little myelosuppression was documented in this heavily pretreated population. Our study had very close monitoring of haematologic status, and it is possible that this study was more sensitive to detect clinically occult myelosuppression, since none of the patients suffered febrile neutropenia or other infectious complications of myelotoxicity. Preliminary data from several studies combining imatinib with chemotherapy have been reported in abstract form.[42–47] In the majority of these studies, significant toxicity was encountered requiring adjustment of dosing below standard range. In some cases, imatinib was used on an intermittent dosing schedule to temper toxicity.[45–47]

The aim of our work was to provide the data upon which future combination trials might be based to assess whether selective tyrosine kinase inhibition with imatinib might contribute additional efficacy to standard chemotherapy. However, as was quickly evident, toxicity of the combinations was more severe than would easily allow for drug administration at reasonably conventional doses. Nonetheless, the preclinical and theoretical rationale to study the combination of imatinib with chemotherapy remains intriguing and may be worthy of further investigation. Strategies to decrease toxicity may include altering drug delivery schedules, or providing additional supportive care with haematopoietic growth factors to mitigate myelosuppression. In designing such studies, close clinical and laboratory monitoring for toxicity is required, along with pharmacokinetics to evaluate for a possible drug-drug interactions as a cause for unexpected side effects.

Conflict of interest statement

Drs. George reports that she has received limited honoraria for invited lectures sponsored by Novartis. Drs. Desai, Eder, Appleman and Ryan have no conflicts to disclose. Dr. Demetri reports that he has served as a consultant for Novartis, and has received limited honoraria for invited lectures sponsored by Novartis.

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