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CLINICAL TRIAL REPORT

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A phase II trial of CI-958 in patients with hormone-refractory prostate cancer

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Abstract *Purpose*: To assess the antitumor activity of the benzothiopyranoindazole CI-958 {5-[(2-aminomethyl)amino]-2-[2-(diethylamino)ethyl]-2H-[l]benzothiopyrano[4,3,2-cd]-indazol-8-ol trihydrochloride} in hormone-resistant prostate carcinoma, using an intravenous dose of 700 mg/m^2 every 3 weeks. *Patients and methods*: Patients eligible for this study had advanced prostate carcinoma that had failed hormonal treatment. Changes in an initially elevated prostate-specific antigen (PSA) level and regression of objectively measurable disease were used as response criteria. *Results*: All 33 patients enrolled were evaluated. Of 30 with elevated PSA levels, 6 had a $>50\%$ decline maintained for >30 days; response durations ranged from 105 to 623 days. Eleven patients had objectively measurable disease; two had partial responses (lasting 316 and 461 days) consisting of shrinkage of retroperitoneal nodes and of masses surrounding the rectum and bladder. The survival of all responding patients ranged from 366 days to 709 days and the median survival of all patients was 12 months (range 1–23 + months). Neutropenia was common, but thrombocytopenia was not. Nonhematologic side effects included nausea, vomiting, anorexia, asthenia, and chills, but were usually mild. The drug caused phlebitis when given into peripheral veins and central venous administration is recommended. No consistent reductions in cardiac function were documented by sequential assessment of left ventricular ejection fractions. *Conclusions*: CI-958 has modest but definite antitumor activity in hormone-resistant prostate carcinoma. Its toxicities include neutropenia, nausea, vomiting, anorexia, asthenia, chills and phlebitis.

Key words Hormone-resistant prostate carcinoma · CI-958 · Chemotherapy

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Introduction

Hormone-refractory prostate carcinoma (HRPC) is highly resistant to most chemotherapy agents. Estramustine, vinblastine, mitoxantrone and doxorubicin occasionally produce objective disease regressions, but these are ordinarily of brief duration and their effects on overall survival are minimal [2]. The development of new agents for this disease is a priority.

The benzothiopyranoindazoles comprise a class of chromophore-modified anthracenediones related to mitoxantrone [6], and CI-958 {5-[(2-aminomethyl)amino]-2-[2-(diethylamino)ethyl]-2H-[l]benzothiopyrano[4,3,2-cd]-indazol-8-ol trihydrochloride} is a member of this group. The mechanism of benzothiopyranoindazole cytotoxicity resembles that of doxorubicin and mitoxantrone. CI-958 intercalates into DNA, as shown by its ability to unwind closed circular DNA [7], and produces single and double strand breaks which are slowly repaired. This suggests that CI-958 stabilizes the cleavable complex of DNA with topoisomerase II.

These compounds have antitumor activity in murine leukemia, transplanted murine epithelial tumors and human tumor xenografts [6]. CI-958 has entered clinical trials. In a phase I trial that used a single intravenous dose of CI-958 every 3 weeks, the dose-limiting toxicities

were neutropenia and renal dysfunction [1]. The recommended phase II dose for patients with minimal or no prior chemotherapy was 700 mg/m^2.

The object of this study was to assess CI-958 activity in patients with HRPC. Because it is often difficult to evaluate prostate cancer responses using standard objective criteria, changes in serum prostate-specific antigen (PSA) levels were used as a surrogate marker for response to treatment. The study included assessment of cardiac function, since CI-958 is structurally similar to older established agents such as mitoxantrone that produce cardiac damage. An explicit goal was to develop a drug with cytotoxic activity and no adverse cardiac effects. The study has previously been reported in abstract form [8].

Patients and methods

Patient selection

Between December 1993 and May 1995, 33 patients were enrolled in this multicenter study. Eligible patients had stage D2 prostate adenocarcinoma with progressive disease following one or more hormonal regimens, serum testosterone level <100 ng/dl, ECOG performance status 0–2, no prior cytotoxic chemotherapy, PSA $>$ 20 ng/ml or bidimensionally measurable disease; and a minimum 2-week interval following discontinuation of flutamide with no evidence of a withdrawal response. Additional eligibility criteria included total bilirubin, serum creatinine, and SGOT values not more than 1.5 times the upper limit of normal, absolute neutrophil count (ANC) $\geqslant$ 1500/μl, platelet count $\geqslant$100,000/μl, and a left ventricular ejection fraction (LVEF) $\geqslant$ 45% by cardiac gated scan. Patients whose prior hormonal therapy included a luteinizing hormone-releasing hormone agonist continued such treatment. All patients signed informed consent forms in accordance with Institutional Review Board procedures.

Patient evaluation

Baseline evaluation included a physical examination, complete blood count (CBC), PSA, urinalysis, multichannel chemistry panel, bone scan, measurement of LVEF by cardiac gated scan, EKG, chest X-radiography, and computed axial tomography (CT) of the abdomen and pelvis if appropriate to document measurable disease. A CBC was repeated at least weekly during therapy, or more often during periods of grade 3 (WBC 1000–1900/μl and/or platelets 25,000–49,000/μl) or 4 (WBC $<$ 1000/μl and/or platelets $<$ 25,000/μl) myelosuppression. PSA, urinalysis and blood chemistries were obtained after each course. Bone scans were repeated after every two courses. CT scans were repeated in patients with measurable disease after every two courses. EKG and cardiac gated scan were repeated after every three courses of treatment and at discontinuation of treatment. Adverse events were recorded according to National Cancer Institute Common Toxicity Criteria.

Response to treatment was based on either changes in an elevated baseline PSA value or on regression of measurable disease. A response based on PSA alone required a $\geqslant$50% reduction from baseline maintained for three consecutive evaluations done at least 3 weeks apart (minimum duration of 6 weeks). For patients with measurable disease, a partial response (PR) required a $\geqslant$50% reduction in the sum of the products of the perpendicular diameters of identified lesions, confirmed on a second assessment done at least 4 weeks later. A complete response (CR) required complete disappearance of all radiographic evidence of disease, confirmed on a second assessment done at least 4 weeks later. Progression was defined as any of the following: PSA increase of $\geqslant$50% above baseline on two successive determinations, a $\geqslant$25% increase in the sum of the products of the perpendicular diameters of measurable lesions, appearance of new soft tissue or bone lesions, or clinical deterioration clearly related to prostate cancer symptoms.

Treatment plan

CI-958 was diluted in 200 to 400 ml 5% dextrose in water and administered intravenously over 2 h. The drug was initially infused into a peripheral vein; because of the development of phlebitis, which was almost universal with this method, the CI-958 was subsequently given via a central vein. The initial CI-958 dose was 700 mg/m^2. Subsequent doses were reduced by 25% for any of the following: ANC nadir from the prior course $<$ 500/μl for 5 days or more, or accompanied by fever or infection; platelet count nadir $<$40,000/μl; or nonhematologic toxicity exceeding grade 2. Initially dose escalation above 700 mg/m^2 was permitted for patients who tolerated CI-958 treatment without limiting toxicity. However, in other CI-958 phase II studies being conducted simultaneously, renal dysfunction occurred at doses $\geqslant$875 mg/m^2. Consequently, all CI-958 phase II protocols were amended to preclude treatment with doses above 700 mg/m^2. Courses were repeated every 3 weeks if hematologic recovery, defined as an ANC $\geqslant$ 1500/μl and platelet count $\geqslant$100,000/μl, had occurred, and nonhematologic adverse events had resolved. There was no maximum number of treatment courses that could be administered. Investigators had the option of suspending ongoing CI-958 treatments in patients who achieved a significant response to treatment. CI-958 treatment was discontinued for progressive disease, unmanageable toxicity, upon patient request, or at individual discretion, if no response had occurred after a minimum of four courses.

Statistical methods

Protocol accrual was planned in two stages. If no responses were observed in the first 14 patients, then the study would be terminated because the true response rate was $<$20% with 95% confidence limits [3]. If this initial cohort included either one PR or CR by measurable disease criteria or three PSA-only responses, then the study would enroll a total of 30 patients with PSA-evaluable disease and 14 patients with measurable disease.

Overall survival was measured from the start of treatment and analyzed by the Kaplan-Meier product-limit method. Time to progression was determined from the start of treatment until withdrawal for disease progression, as defined above. Duration of PSA response was also described as the interval between the first day that the PSA decreased to $\leqslant$50% of the baseline value until the first day that the PSA increased to $\geqslant$50% above the lowest value achieved and was above normal.

Results

Baseline characteristics

All of 33 patients registered for the study received CI-958 treatment and were included in the efficacy and safety results. Their pretreatment characteristics are given in Table 1. Of the 33 patients, 22 had only an elevated PSA to follow, 3 had only objectively measurable disease with no PSA elevation, and 8 had both measurable disease and an elevated baseline PSA. The three patients with no PSA elevation all had the diagnosis of poorly differentiated adenocarcinoma made by biopsy of the prostate gland with Gleason scores of 7, 8 and 8, respectively, and had no evidence of other primary. Most (29) of the patients had been treated with flutamide prior to enrollment. The median interval

Table 1 Baseline patient characteristics (*LHRH* luteinizing hormone-releasing hormone)

No. of patients enrolled/treated	33
Age (years)	
Median	70
Range	43–82
Performance status	
0	17
1	13
2	3
Prior therapy	
Radiotherapy	22
Prostate	10
Palliative to bone	16[a]
Orchiectomy/LHRH agonist	33
Antiandrogen	29
Prostatectomy	3
Elevated PSA (ng/ml)	
20–100	13
101–500	12
> 501	5
Total	30
Measurable disease	11

[a] Four had more than one course

between the last flutamide dose and the first CI-958 dose was 109 days (range 14 days to 32 months). Clear radiologic or PSA evidence of stable or progressing disease was required following recent discontinuation of flutamide.

Response data

Of 30 patients, 6 (20%; 95% confidence interval, 6 to 34%) with elevated baseline PSA values met the criteria for PSA response. The maximum percentage PSA reductions in these patients were: 99%, 99%, 99%, 95%, 70%, and 60%. PSA values fell to $\leqslant$4.0 ng/ml in three patients from baseline values of 39.8, 148.9 and 358.4 ng/ml. The onset of the PSA response occurred after the first CI-958 treatment in two patients, after the second, third, and fourth treatments in one patient each, and after the ninth treatment in one patient. The PSA responses ranged in duration from 105 to 623 days (Table 2). All six PSA responses had ended at the time of writing. Two responding patients developed rising PSA values while receiving CI-958 treatments, and CI-958 was discontinued in these patients. Four responding patients had their CI-958 treatments suspended while in response after completing 8 (three patients) and 12 treatment courses (one patient), and the unmaintained responses continued for 112, 175, 231 and 399 days. CI-958 treatment was reinstituted in two patients at the point of progression, but was without effect.

Of 11 patients with measurable disease, two (18%) responded (Table 2, Fig. 1). Patient 1 had marked reduction of retroperitoneal adenopathy, a decrease in thickening of bladder and rectosigmoid walls, and an unequivocal improvement in bone scan, which lasted 316 days. He also had a 99% reduction in PSA values, which lasted 203 days. Patient 10 was treated with ten cycles of drug over 8 months, by which time his measurable retroperitoneal adenopathy had shrunk by approximately 75% and a 6.0×3.0 cm retrovesical mass had become almost undetectable. He then remained off of CI-958 for another 6 months, after which his PSA rose again and the retrovesical mass recurred. CI-958 was restarted, but was without effect. The total duration of response, including time on and off treatment, was 461 days. He also had a maximum PSA reduction of 58%, but did not qualify as a PSA responder because the decrease was not sustained over three consecutive measurements.

Time to progression and survival data

All patients had progressed or died at the time of writing. The median time from start of treatment to progression was 334 days (range 134–644 days). The

Table 2 Characteristics of responding patients

Patient	Response criteria	PSA			PSA response				
		Baseline (ng/ml)	Nadir (ng/ml)	Decrease (%)	Time to progression (days)[a]	Duration (days)[b]	Continued response (days)[c]	Measurable disease response (days)	Survival (days)
1	PSA + measurable disease	358.4	3.9	99	267	203	175	316	557
4	PSA only	34.5	0.5	99	279	238	112		454
10	PSA + measurable disease	184.0	78	58[d]	461			461	603
11	PSA only	148.9	0.1	99	645	623	399		670+
15	PSA only	42.3	12.5	70	334	123			709
17	PSA + measurable disease	4998.0	1985.0	60	127	105		Stable during PSA response	366
21	PSA only	366	6.6	98	428	343	231		495

[a] Measured from start of treatment
[b] Measured from first documentation of response
[c] Duration of continued response after drug was stopped
[d] The decline in this patient's PSA was not sufficiently sustained to meet the criteria for a PSA response; however, the decline in his PSA level coincided with his measurable disease response

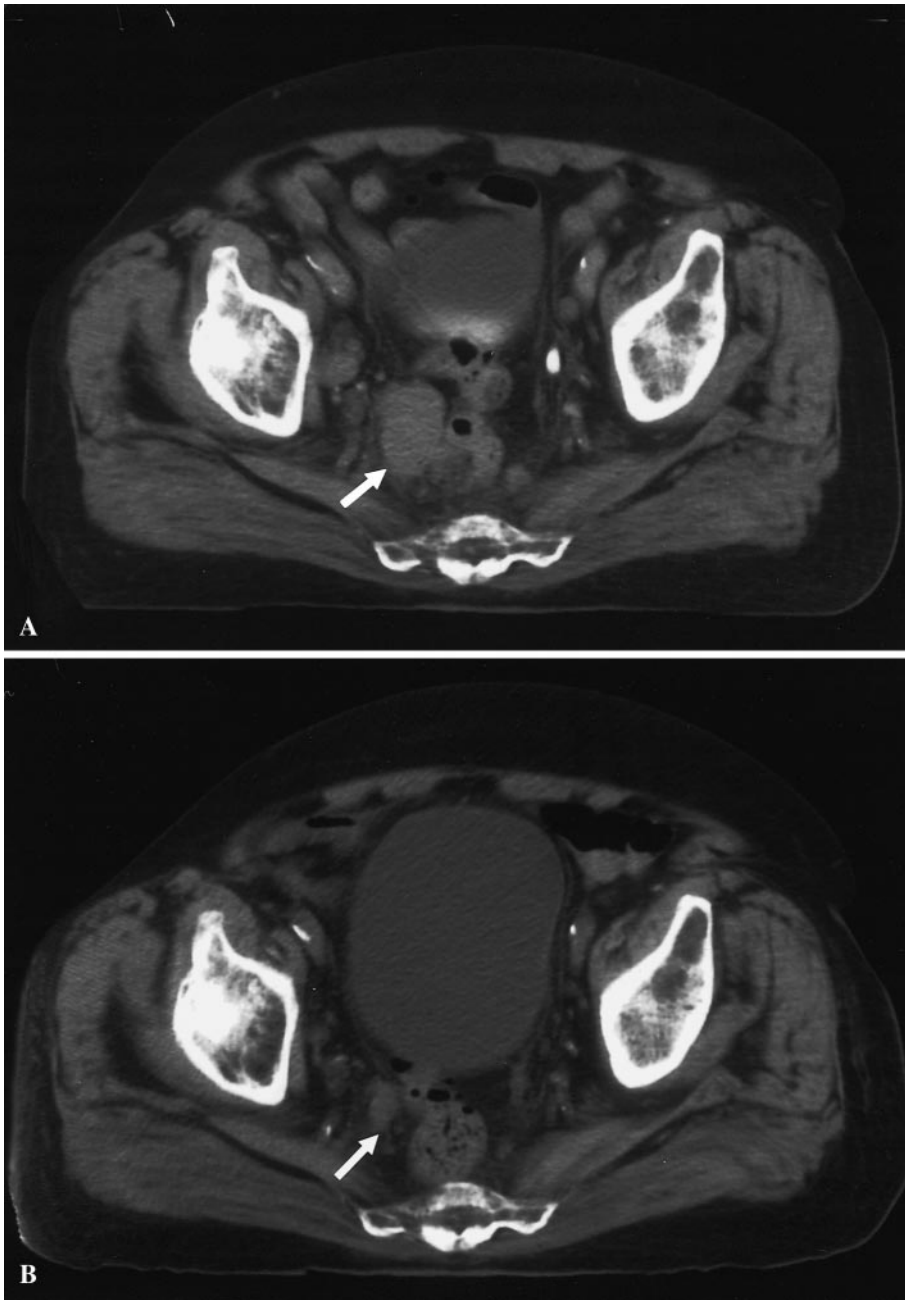

Fig. 1 **A** CT scan of patient 1 at beginning of treatment, showing perirectal mass (*arrow*). **B** CT scan of same patient after six cycles of CI-958, showing reduction in the size of the tumor

median survival duration was 12 months (range 1 to 23 + months). The median survival duration of the seven responders was 557 days (range 366–709 days). At last follow-up, seven patients were still alive or were lost to follow-up alive.

Toxicity

The CI-958 dose of 700 mg/m^2 every 3 weeks was generally well tolerated. A total of 201 treatment courses were administered (median 6 courses per patient, range 1 to 16) and five patients received 10 or more courses. CI-958 dose adjustments were based on myelosuppression or other adverse events reported during the prior course. Hematopoietic growth factors were not used to sustain or intensify the dose to be administered. In the 168 courses administered beyond course 1, 700 mg/m^2 was administered in 139 courses (83%). Dose reductions were necessary in eight patients: prior neutropenia (three), fever or infection while neutropenic (three), renal dysfunction (one), and thrombocytopenia unrelated to CI-958 treatment (one).

Drug-related neutropenia was common: 74% of all treatment courses were associated with an ANC nadir of grade 2 (23%), grade 3 (31%), or grade 4 (20%). The median ANC nadir was 988/μl. The median day of the ANC nadir was day 15, with recovery to values

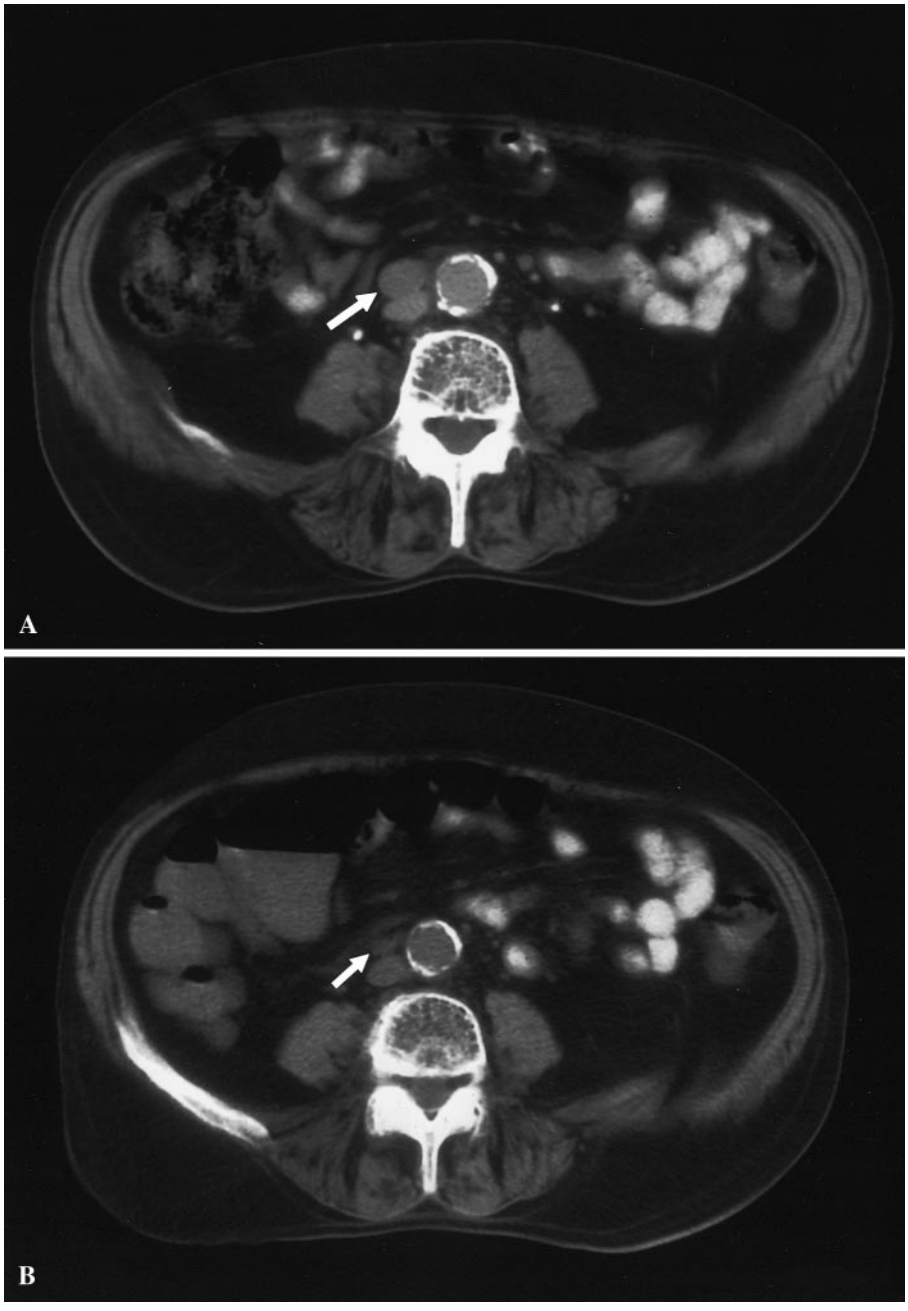

Fig. 2 **A** CT scan of patient 10 at beginning of treatment, showing periaortic adenopathy (*arrow*). **B** CT scan of same patient after six cycles of CI-958, showing reduction in the size of the node

exceeding 1500/μl by day 19, allowing retreatment on schedule. Six patients were hospitalized while neutropenic, two for fever and four for documented infection; they all recovered.

Thrombocytopenia was uncommon. Of all treatment courses, 9% were associated with a platelet count nadir of grade 2 (4%), grade 3 (4%), or grade 4 (1%). One patient with a history of hematuria due to bladder involvement was hospitalized for worsening hematuria during thrombocytopenia following CI-958 treatment. Two patients received platelet transfusions.

Nonhematologic treatment-related adverse events were frequent but usually were only grade 1 or grade 2 in intensity. The most common of these were nausea (39% of patients), fever usually occurring within 24 h of dosing (36%), asthenia (30%), chills (24%), vomiting (24%), and anorexia (15%). CI-958 also commonly caused phlebitis after infusion into peripheral veins, a problem that was eliminated by central vein administration. Three patients were hospitalized for treatment-related adverse events unrelated to neutropenia, i.e. fever and chills during the evening after receiving a CI-958 treatment, shortness of breath on the day of treatment, and deep vein thrombosis following an episode of phlebitis. One patient developed recurrent proteinuria and moderate elevations in serum BUN and creatinine with repeated treatment. These changes were reversible between courses.

Two unusual types of adverse events occurred during CI-958 treatment. First, some patients experienced a sense of warmth, tingling, burning, flushing, itching, hives, or numbness, principally in the head, neck, face or trunk areas during infusions. These reactions were self-limiting and appeared to be related to the rate of drug administration. They tended to occur during early treatment courses and not recur upon subsequent exposures. Second, CI-958 treatment was associated with reactions involving the tips and nails of the fingers and toes, usually involving discoloration of nail beds, tenderness or swelling of fingertips, and possibly loss of the nail.

All patients entered the protocol with an LVEF measured at $\geqslant$45%. Five patients with rapidly progressive disease were withdrawn early and did not have repeat scans. A total of 63 follow-up cardiac gated scans were performed in 28 patients (median two scans per patient, range one to six).

The average LVEF value at baseline and following completion of three courses, six courses, and (for patients who received seven or more courses) the final course was 61.4% ($n = 28$), 60.6% ($n = 26$), 57.9% ($n = 15$), and 58.8% ($n = 10$). Two patients had a follow-up cardiac gated scan at some time during the study which demonstrated a $\geqslant$10% decrease in LVEF compared with their baseline and was to a value below normal (50%). One 79-year-old patient had a decrease in LVEF from 60% at baseline to 52% after three courses and to 46% after six courses of treatment. The last scan showed mild global hypokinesis with a mildly dilated left ventricle. The patient remained asymptomatic. A second patient, also 79 years old, developed symptoms of congestive heart failure after six courses of treatment, in association with a measured LVEF of 34%. His prior values were 45% at baseline and 40% after three courses. His last scan showed global hypokinesis with an enlarged left ventricle. The consulting cardiologist felt that these changes were due to coexisting medical conditions and not to CI-958 treatment. This patient died 8 months later from cardiac failure.

Discussion

After doxorubicin and other anthracyclines were recognized as active antineoplastic agents, several drug development programs examined newer classes of compounds that would simultaneously preserve DNA-intercalating ability and eliminate cardiac toxicity as a side effect. The anthracenediones, for example mitoxantrone, were early candidates as possible successors to the anthracyclines [10]. A further route of drug development, leading to the synthesis of both the anthrapyrazoles [5, 9] and the benzothiopyranoindazoles [6], focussed on modification of the quinone group on the central ring of the anthracyclines and anthracenediones, since that chemical structure is regarded as pivotal to the mechanism of cardiac toxicity. The anthrapyrazoles are chromophore-modified anthracenediones whose design involved modification of the central quinone moiety to a quasi-iminoquinone [5]. This markedly reduces superoxide dismutase-sensitive oxygen consumption in comparison to doxorubicin, and also increases resistance to electrochemical reduction, both of which should reduce redox cycling and cardiac damage. The further chemical modification of the anthrapyrazoles to produce benzothiopyranoindazoles [6] involves replacement of the carbonyl group at the 6 position of the central anthrapyrazole ring with sulfur. This virtually eliminates the possibility of redox cycling and subsequent in vivo radical formation

A large series of benzothiopyranoindazoles has been synthesized and screened, and the structure-activity criteria for biological activity in murine L1210 leukemia, P388 leukemia and B-16 melanoma have been defined [6]. CI-958 is a member of that group and has sufficiently favorable characteristics for it to have been selected for clinical development. It has an IC_{50} of 7.1×10^{-8} M against L1210 leukemia, a %T/C of 280 against P388 leukemia and a %T/C of 281 against B-16 melanoma [%T/C = (median survival of treated animals/median survival of control animals) $\times$ 100]. It can fragment DNA, consistent with stabilization of the cleavable complex of topoisomerase II, although this point has not been formally proved.

In a phase I trial that used a single intravenous dose of CI-958 every 3 weeks [1], the toxicity consisted of dose-related myelosuppression, and of renal and liver toxicity. Neutropenia occurred at doses above 300 mg/m^2 and was dose-limiting in four of nine patients treated at 700 mg/m^2. Nadir neutrophil counts were reached at a median of 14 days after treatment and recovered by day 22. Thrombocytopenia was not a problem. Severe renal, or renal plus liver toxicity developed in two patients treated at 875 mg/m^2. The drug pharmacokinetics were multiphasic, with a rapid initial clearance and a prolonged terminal phase having a mean duration of 7.7 days, when measured by high-performance liquid chromatography. The recommended phase II dose for patients with minimal or no prior chemotherapy was 700 mg/m^2. Because of the severe hepatic and renal toxicity that can occur at a CI-958 dose of 875 mg/m^2, the 700 mg/m^2 level was close to the maximum tolerated dose.

Thus, the critical points for evaluation of CI-958 and related compounds in phase II trials are both their antitumor activity and their patterns of toxicity, with particular attention being paid to neutropenia, renal and hepatic toxicity, and cardiac damage. The present study demonstrated definite activity of CI-958 in prostate carcinoma; the two responses in measurable disease produced almost complete resolution of bulky tumor.

The toxicity pattern of CI-958 was similar to that predicted by phase I studies [1]. The renal toxicity encountered in one patient was reversible, but suggested that further dose escalation could lead to more serious problems, as had been observed in other trials [1]. The dose of 700 mg/m^2 is therefore close to the maximum

tolerated dose of CI-958. The cardiac toxicity of the anthracyclines is mediated by oxygen free radicals produced by reaction with an iron-doxorubicin reducing complex. Preclinical data have shown that CI-958 is 20-fold less active than doxorubicin in stimulating superoxide dismutase-sensitive oxygen consumption, a measure of superoxide radical formation [4]. The clinical data did not document any consistent fall in cardiac function, and support the hypothesis that CI-958 has less cardiac toxicity than doxorubicin.

In conclusion, these findings demonstrate an antitumor effect of CI-958 in prostate adenocarcinoma. Further development of the drug will depend on the balance between benefit and a somewhat limiting toxicity profile.

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