A Phase II Study of Oral Idarubicin as a Treatment for Metastatic Hormone-Refractory Prostate Carcinoma with Special Focus on Prostate Specific Antigen Doubling Time

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BACKGROUND. Treatment of hormone-refractory prostate carcinoma with chemotherapy is purely palliative, and reported response rates have been low. At the time this study was conducted, there was an urgent need for a trial using potentially efficacious drugs, with quality of life (QL), and serial prostate specific antigen (PSA) behavior as endpoints.

METHODS. In this Swiss multicenter Phase II study, 30 patients were enrolled to receive oral idarubicin. Patients were administered 35 mg idarubicin on Days 1 and 8 of each cycle, and treatment was repeated every 3 weeks. Assessment was based on response rates, sequential PSA measurements in serum, toxicity, and selected aspects of QL.

RESULTS. Twenty-six of 30 patients were evaluable for response, and none of them achieved a response. Three patients had stable disease as their best response, and their PSA levels also remained stable. In all other patients, PSA increased exponentially over time; the median PSA doubling time was 2.1 months (mean, 2.6; range, 0.7–6.1). Toxicity was minimal and consisted mainly of myelosuppression and nausea/vomiting. QL did not change significantly during therapy with regard to general well-being, fatigue, or nausea/vomiting. However, there were improvements in patient-rated and physician-rated pain.

CONCLUSIONS. At the dose and schedule used in this study, oral idarubicin showed only minimal efficacy against hormone-refractory prostate carcinoma. In patients who did not respond, PSA doubling times were similar to those in patients who relapsed while receiving only antiandrogen therapy. In future clinical trials, QL and serial PSA behavior should be included in analysis. ***Cancer* 1997;79:1703–9.**
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KEYWORDS: prostate carcinoma, hormone resistance, chemotherapy, idarubicin, prostate specific antigen, prostate specific antigen doubling time, quality of life.

Adenocarcinoma of the prostate is the most commonly diagnosed visceral malignancy among men in the United States and is second only to lung carcinoma as a cause of cancer death.[1] At the time of diagnosis, at least two-thirds of all patients already have non-organ-confined disease and are therefore not amenable to curative treatment.[2] These patients will eventually be faced with problems of the lower urinary tract and/or distant metastases, and hormonal therapy remains the gold standard in such cases. Suppression of testicular androgens, alone or in combination with peripheral androgen receptor blockade, is the most effective palliation, with retardation of tumor growth achieved in 70–80% of patients.[2] Progressive disease eventu-

ally occurs due to androgen-independent cell lines, for which chemotherapeutic agents are urgently needed.

The role of chemotherapy in the treatment of prostate carcinoma is not yet established. Less than 10% of patients with hormone-refractory metastatic disease treated with various drugs experience complete or partial response.[3] Moreover, the duration of such responses is short-lived, and toxicity is considerably high. Many patients are offered second-line therapy at a time when their general condition has already deteriorated. Finally, the biology of prostate carcinoma is such that even advanced tumors have a long median doubling time of 8 months,[4] whereas cytotoxic agents are effective against rapidly dividing cells.

The Swiss Group for Clinical Cancer Research established a master protocol for Phase II trials in order to evaluate the efficacy of chemotherapeutic drugs in the treatment of hormone-refractory prostatic carcinoma. Idarubicin, when given orally, has a higher bioavailability and a lower cardiac toxicity than other anthracyclines and was therefore selected as a promising drug for clinical investigation. This report details trial results with respect to response, toxicity, quality of life (QL), and prostate specific antigen (PSA) doubling time.

PATIENTS AND METHODS

Patient Selection

Between October 1993 and April 1995, 30 eligible patients with metastatic prostate carcinoma were enrolled in this study. All patients had progressive disease after hormonal therapy: 25 had a bilateral orchiectomy and 3 received a luteinizing hormone-releasing hormone (LH-RH) agonist, which was continued during chemotherapy. Two patients had a maximal androgen blockade. The antiandrogen therapy was discontinued before idarubicin was given, and no withdrawal syndrome could be observed in those two patients. In addition, four patients had been treated with palliative radiotherapy, but not less than 4 weeks prior to study entry. More patient characteristics are outlined in Table 1.

Eligibility criteria included the following: a life expectancy of at least 3 months, continuation of LH-RH analogue, adequate renal function (serum creatinine less than 150 mmol/L) and hepatic function (bilirubin less than 30 mmol/L), and sufficient bone marrow reserve (granulocytes greater than or equal to 3.5×10^9/L, platelets greater than or equal to 100×10^9/L). PSA was measured with a monoclonal radioimmunometric solid phase assay (Hybritech; upper norm value, 4 ng/mL). The trial had been approved by local ethical committees, and written informed consent was obtained from each patient prior to study entry.

TABLE 1
Patient Characteristics at Trial Entry

Age	
Median	72
Range	51–79
Performance status	
0	11
1	13
2	4
3	2
Tumor localization	
Lymph nodes and liver	1
Bone alone	17
Bone plus:	
Lymph nodes	7
Liver and lymph nodes	1
Lung, liver, and lymph nodes	1
Lung and pleura	1
Lung and lymph nodes	1
Lymph nodes and bladder	1
Measurable lesions	
No	17
Yes	13
Total	30

Patients older than 80 years, patients with severe heart disease, and patients who had received radiotherapy less than 4 weeks prior to the beginning of the protocol were not eligible, nor were patients with prior cytotoxic therapy, including estramustine phosphate sodium.

Treatment

Idarubicin (4-demethoxy-daunorubicin) was provided by Farmitalia Carlo Erba AG, Zug, Switzerland, as capsules of 5, 10, and 25 mg. Patients were administered 35 mg idarubicin orally on Days 1 and 8 of each cycle, and treatment was repeated every 3 weeks. A maximum of 11 cycles was allowed in order to restrict the total cumulative dose to 770 mg. Dosage modification was based on the nadir of granulocytes and platelets during the first two cycles. Treatment was to be discontinued in cases of patient refusal, deterioration of renal or hepatic function, toxicities that were Grade 3 or 4 according to World Health Organization (WHO) criteria, and progression of disease.

Assessment

Pretreatment evaluation included medical history, physical examination, complete blood count, serum chemistry, and measurement of serum PSA, and was repeated at the start of each new cycle. Radiologic examinations consisted of bone scan; bone X-ray, if applicable; computed tomography scan of the abdomen; and chest X-ray. In cases of measurable lesions,

radiographic studies were conducted every 3 weeks. Electrocardiography and determination of left ventricular ejection fraction were performed at study entry. For patients with measurable metastases, the criteria of the European Organization for Research and Treatment of Cancer (EORTC) were applied. In patients with unmeasurable disease, response was defined as follows: no increase in the size of the primary tumor, no appearance of new metastases, no increase of prostate acid phosphatase or PSA, and improvement of tumor-related pain by at least two grades on the WHO 5-grade scale (none, mild, moderate, severe, intolerable). Serial PSA values as secondary trial endpoints were evaluated in a prospective fashion, according to the definitions of Seidman et al.[5] Patients were required to have had a minimum of two courses of chemotherapy in order to be evaluable for response. Toxicity was assessed according to WHO criteria.[6]

Selected aspects of QL were assessed with a short self-report questionnaire for patients, based on an early version of the EORTC questionnaire.[7] In consideration of the small sample size, a few items and scales were selected according to their relevance to the study question[8,9] and based on expert judgment and psychometric performance (sensitivity to course of disease and treatment) in a previous small cell lung carcinoma trial.[10,11] Reliability and validity criteria suggested by Aaronson et al.[7] were tested and confirmed overall as well as separately for each of the three languages of the sample (German, French, and Italian).[10] The questionnaire items regarding appetite, pain, fatigue, and nausea/vomiting correspond to those of EORTC QLQ-C30,[12] which was published and ready for use only after this trial was designed.

The questionnaire is summarized in Table 2. It included single items for functional status (2 items, binary response format: yes/no), appetite, pain, pain medication, pain relief, and multi-item scales for fatigue (3 items) and nausea/vomiting (2 items). All symptom scales were in a 4-point response format (not at all/a little/quite a bit/very much). They had a range from 1 to 4, with lower scores indicating lesser symptoms. A global indicator for general well-being[10] was also included (7-point scale: very poor to excellent). It had a range from 1 to 7, with higher scores indicating better well-being; its sensitivity to tumor-related symptoms and chemotherapy side-effects was confirmed a study of small cell lung carcinoma patients.[13] In addition, open questions were asked regarding pain location, time of pain onset and duration, and further complaints. The time frame was related to the past week. The two multi-item scales were summarized by mean values. Pain, fatigue, and general well-being were used as primary endpoints; the other measures were used for descriptive purposes only.

The questionnaire was completed on Day 1 (baseline) and Day 8 (short-term toxicity) and on Day 1 of each additional cycle, as well as at the time of treatment failure. The WHO scale for pain medication and registration of complementary pain medication was also requested and was to be filled in before therapy was given.

Statistical Methods

The results of the trial were presented in tables and graphs. No formal statistical tests were used. Sequential PSA values for all evaluable patients were plotted as curves on a log scale, which allows identification of the longitudinal development of each patient. The QL and pain measures were descriptively evaluated on the basis of individual differences between each score at baseline and subsequent assessments by Wilcoxon's signed rank test. QL was evaluated only up to Month 4, because too few patients were left thereafter due to attrition.

RESULTS

The 30 eligible patients received a total of 122 cycles (median per patient, 3 cycles; range, 1–11 cycles). Four patients were not evaluable for response; 3 of them had only one treatment cycle, and 1 patient died at the beginning of Cycle 3 and could not be assessed for response. Of the 26 evaluable patients, 13 had measurable disease and 13 had unmeasurable disease (Table 3). One patient had a minor eligibility violation (creatinine 169 mmol/L at study entry) but was still analyzed.

Response to Therapy

None of the 26 evaluable patients achieved a response (Table 3). Three patients with measurable lesions had stable disease as their best response; 1 of them experienced no change in disease for the maximum of 11 cycles, 1 was stable at Cycle 3 and progressed during Cycle 5, and 1 had progressive disease after Cycle 3.

Of the 13 patients with unmeasurable disease, 11 progressed, 1 refused further therapy after 5 cycles, and 1 was taken off treatment at Cycle 7 due to low granulocytes and platelets. Median PSA at study entry was 174 ng/mL (range, 1–3410 ng/mL). Serial PSA values of evaluable patients are shown in Figure 1. Except for the three patients with measurable disease who remained stable, logarithmic (log) PSA levels increased linearly during treatment, which corresponded to an exponential rise and therefore allowed for calculation of PSA doubling time according to the following formula:[4]

TABLE 2
Domains and Items of the Quality of Life Questionnaire[a]

General domains	
Functional status	Do you have any trouble taking a short walk?
	Do you have to stay in a bed or a chair for most of the day?
Fatigue	Did you need to rest?
	Have you felt weak?
	Were you tired?
General well-being	How would you rate your general well-being during the past week?
Tumor symptoms	
Pain	Have you had pain during the past week?
	If yes, where?
Pain medication	Did you take any pain killers?
Relief by pain medication	If yes, how much was your pain relieved?
Further complaints	Have you had any other complaints during the past week?
Toxicity	
Appetite disturbance	Have you lacked appetite?
Nausea and vomiting	Have you felt nauseated?
	Have you vomited?

[a] For time frame and response format, see description in the "Patients and Methods" section of the article.

TABLE 3
Observed Best Response to Therapy

Response	No. of patients
Measurable disease	
No change	3
Progression	10
Unmeasurable disease	
No response	13
Evaluable patients	26

$$\text{PSA doubling time} = \frac{(\log 2) \times t}{\log(\text{final PSA}) - \log(\text{initial PSA})},$$

where t is the time form initial to final PSA determination. Median PSA doubling time was 2.1 months (mean, 2.6 months; range, 0.7–6.1 months).

Four patients died while receiving treatment. Three of these deaths were tumor-related. A patient age 77 years with a PSA of 3000 at study entry died after the first cycle, presumably from cardiac failure, but the exact cause of death could not be ascertained because no autopsy was performed.

Toxicity

All 30 patients were evaluable for toxicity. Overall, oral idarubicin was well tolerated, with no drug-related mortality. The primary toxicities were myelosuppression and nausea/vomiting (Table 4). Three patients had Grade 3 granulocytopenia (absolute granulocyte count, $1.1–1.9 \times 10^9$/L); one of them had also thrombocytopenia (absolute platelet count, 74×10^9/L) and was removed from the study. One patient had a cardiac insufficiency of Grade 2 in Cycle 1, and an agranulocytosis (WHO Grade 4) was noted shortly after that cycle. The patient was removed from the study and died of the tumor 10 days later. Other toxicities included loss of appetite (Grade 1 and Grade 2), metallic taste (Grade 1), obstipation (Grade 2), dermatitis (Grade 1), and esophagitis (Grade 3). Neither renal nor neurologic toxicities were observed.

Quality of Life

One hundred seventy one of 206 expected questionnaires (83%) were received at different times: at baseline, during treatment, or at treatment failure. At baseline, 29 of 30 patients filled in the questionnaire. At treatment failure, 23 of 26 expected questionnaires were collected. Due to early treatment failure, the number of patients who provided QL data decreased considerably with time.

The analysis of QL data was restricted to the 26 patients evaluable for clinical response. At baseline, 28% (7 of 25 patients) reported difficulties in walking a short distance, and 20% (5 of 25) indicated that they were confined to a bed or a chair most of the time. These rates did not change appreciably over the whole duration of treatment and were similar at treatment failure.

Both nausea/vomiting (mean at baseline = 1.2, standard deviation [SD] −0.5, n = 25) and fatigue (mean at baseline = 2.3, SD = 1.0, n = 25) were stable

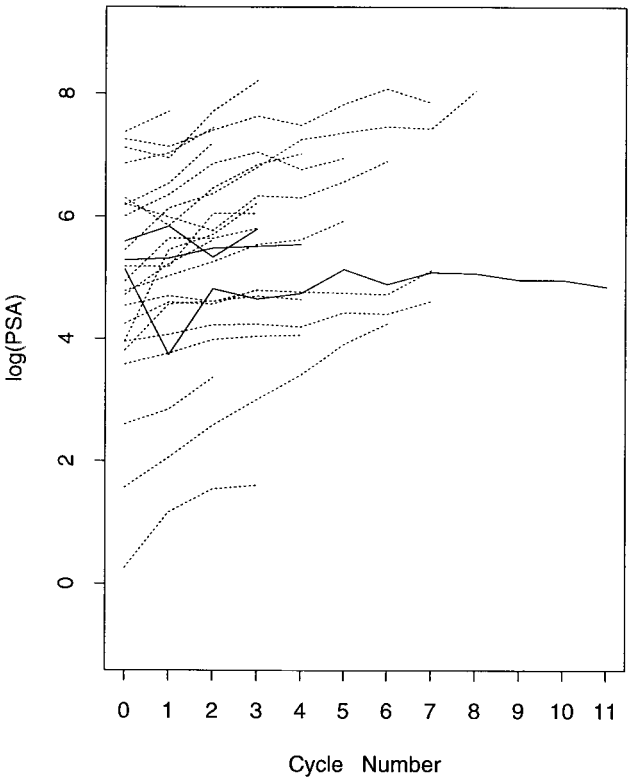

FIGURE 1. Longitudinal development of prostate specific antigen (PSA) values in each evaluable patient is shown. The solid lines represent three patients with measurable, stable disease. log = logarithmic.

TABLE 4
Maximal Observed Toxicities over All Cycles (Number of Patients)

	WHO grade			
Toxicity	**1**	**2**	**3**	**4**
Stomatitis	1	—	1	—
Diarrhea	3	1	—	—
Nausea/Vomiting	10	3	—	—
Alopecia	3	—	—	—
Renal	—	—	—	—
Neurologic	—	—	—	—
Cardiac	—	1	1	—
Hematologic	6	7	3	1
Other	3	4	3	—
WBC (10^9/L)[a]		3.95 (1.1–15.9)		
Thrombocytes (10^9/L)[a]		200 (109–395)		

[a] Median nadir during first cycle (range).
WBC: white blood cell count.

or worse during treatment and at treatment failure, compared with baseline. General well-being (mean at baseline = 4.5, SD = 1.6, n = 24) was stable during treatment and was worsening at treatment failure (mean difference = −0.8, $P = 0.03$, n = 17). In contrast, patient-rated pain (mean at baseline = 2.8, SD 1.1, n = 25) improved during treatment, with a significant change 1 month after baseline (mean difference = −0.6, $P = 0.002$, n = 24); at treatment failure it worsened again (Fig. 2). Similarly, physician-rated pain (mean at baseline = 1.7, SD = 1.1, n = 26) improved during treatment, with significant changes after 2 months (mean difference = −0.6, $P = 0.03$, n = 24) and 3 months (mean difference = −0.7, $P = 0.03$, n = 17) (Fig. 2); these P values cannot be interpreted as strict evidence because they stem from multiple tests of the same variables.

DISCUSSION

Hormone-refractory prostate carcinoma remains a therapeutic challenge for several reasons. Even advanced tumors have a low proliferation rate,[14] which results clinically in a long median doubling time of up to 8 months.[4] Most patients are selected for cytotoxic therapy only at a time when their general condition has already deteriorated. Definition of progression after androgen deprivation is crucial for the assessment of the efficacy of further therapy. Once progression has occurred, no treatment strategy will influence the survival of patients. A definition of progression should therefore include palliative endpoints; otherwise, there would be no need for secondary therapy. Finally, assessment of the effectiveness of chemotherapeutic agents in the treatment of prostate carcinoma is difficult, especially because the standard criteria for the evaluation of response in solid tumors are of limited value. Up to 90% of patients have sclerotic bone metastases only, which are not assessable by classic Phase II response criteria.[15] The remaining 10% of patients, who present with measurable soft tissue masses, may not be representative, because regression of soft tissue and visceral lesions is not necessarily accompanied by reduction of bone metastases.

The objective of this study was to evaluate the efficacy of idarubicin in hormone-resistant prostate carcinoma. Compared with other anthracyclines, idarubicin is less cardiotoxic[16] and has a higher bioavailability, thus making it an ideal candidate for oral administration on an outpatient basis. The rationale for weekly intervals is based on the findings that anthracyclines only affect dividing cells and that after the deaths of these tumor cells, cells from the G_0 phase will be recruited to restore the pretreatment growth fraction of the tumor. At this time, the former G_0 cells undergo cell division and can be targeted again. In our protocol, to prevent dose reduction due to myelo-

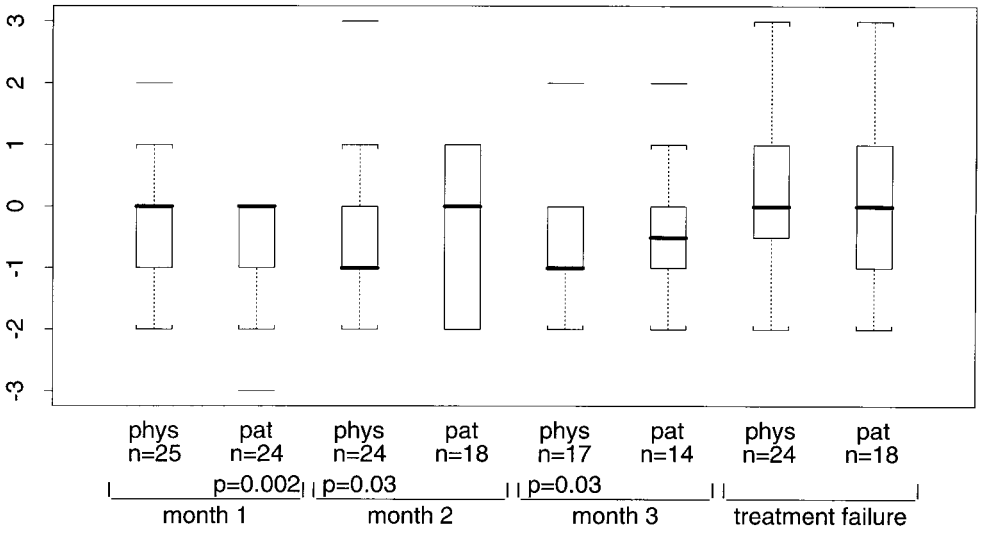

FIGURE 2. Box plots of change in pain scores are shown, from baseline to assessments after 1, 2, and 3 months and at the time of treatment failure. The limits of the "box" give the interquartile range, and the median is symbolized by the bar within the box. The "whiskers" (dotted lines) extend to the minimum and maximum, except for values outside a whisker length of 1.5 × interquartile range, which are marked by a horizontal bar. Negative values indicate improvement from baseline; positive values indicate more pain. Phys: physician-rated pain; pat: patient-rated pain. *P* values are from Wilcoxon's signed rank tests without adjustment for multiple tests and indicate significant deviation from zero.

suppression, every third administration of idarubicin was omitted.

The results with regard to response were disappointing (Table 3). Only 3 of 26 evaluable patients remained stable, and only for a limited period of time. Madsen et al. reported on a Phase II study of weekly administration of 30 mg of oral idarubicin.[17] Ten of 22 patients had stable disease, which was defined as no progress within the first 3 months. However, it must be emphasized that the follow up of the patients in that study did not include the measurement of PSA. It has been suggested that serial PSA measurements may be used as a surrogate endpoint in the evaluation of the efficacy of cytotoxic drugs against hormone-resistant prostate carcinoma.[18] In the current series, all three patients with measurable lesions who had stable disease also experienced stable PSA values, whereas in the other patients PSA increased exponentially (Fig. 1). This log-linear increase in PSA has been demonstrated for the first time in untreated patients with prostate carcinoma,[4] and it has also been observed in patients who relapsed after radical prostatectomy, radiation therapy, and hormonal treatment, respectively.[19] The median PSA doubling time of 2.1 months observed in this study is very similar to that in patients who progress under antiandrogen therapy, suggesting that idarubicin has no effect at all in these patients. After a prospective evaluation and interim analysis, as foreseen by the protocol, this trial was stopped early due to lack of response.

The toxicity was minimal and consisted mainly of myelosuppression (Table 4). As in the study of Madsen et al.,[17] granulocytopenia was more pronounced than thrombocytopenia, but the overall hematologic toxicity was lower in our trial (WHO Grade 3 and 4, 13% vs. 20%). This could be due to our study design, which omitted administration of the drug every third week in order to restore bone marrow function. WHO Grade 3 nausea/vomiting was observed in none of our patients, compared with 48% of patients in the study of Madsen et al.[17]

Overall, in correspondence with the clinical findings, the selected QL indicators showed little or no effect in terms of palliation. The improvement in both patient-rated and physician-rated pain likely reflects some palliation caused by idarubicin, although this could have been confounded by the use of analgesics (Fig. 2).

In a Phase II trial, the number of QL endpoints must be kept to a minimum when the sample size is small. We selected pain, fatigue, and general well-being as key endpoints in the evaluation of these patients.[8,9,20] These measures were not specifically developed for patients with advanced prostate carcinoma. Our findings might therefore reflect a lack of sensitivity. This is not very likely, however, given that the same criteria have been successfully used in many clinical

cancer trials as part of the standard EORTC QLQ-C30 questionnaire.

Our pragmatic approach had its limitations. The selected indicators could not fully encompass the patients' experience. However, there is a clear-cut need for further development of palliative endpoints in the evaluation of patients with advanced prostate carcinoma,[21] and these endpoints should also be suitable for small Phase II trials. We will address this issue in larger samples with a more comprehensive and standard QL assessment.

In summary, oral idarubicin at the dose and schedule used in this study showed only minimal efficacy in the treatment of hormone-refractory prostate carcinoma. In future clinical trials of chemotherapeutic agents, QL and serial PSA behavior should always be included in analysis.

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