Vinorelbine-based Chemotherapy in Hormone-refractory Prostate Cancer

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Abstract. *Background: No consensus exists regarding further therapy for the management of hormone-refractory prostate cancer. In this phase II study, the combination of Vinorelbine with 5-Fluorouracil and folinic acid (FLN regimen) was evaluated in patients with progressive or resistant disease after hormone therapy. Patients and Methods: Thirty-four patients were treated with Vinorelbine at a dose of 20 mg/m^2 intravenously (i.v.) on days 1 and 3, folinic acid (FA), 100 mg/m^2 i.v. and 5-Fluorouracil (5-FU), 350 mg/m^2 i.v. as a short infusion on days 1 to 3. The therapy was given in an out-patient setting, every 3 weeks. Results: All of the 34 eligible patients were evaluable for toxicity and 30 for activity. A total of 127 cycles was administered (91% at full dose). Among the15 patients with measurable disease, four had a partial response (26.6%; C.I. 95%, 28.3% to 65.7%) and four achieved stable disease. In 14 patients (47%) a clinical benefit was documented. Six out of 15 patients with bone-only involvement had stable disease (40%). The median duration of stabilization and partial response was 16 weeks (range 4-24 weeks). The most common toxicity was hematological: Grade 4 (NCI-CTC scale) in five patients at re-cycle. Other toxicities were of low incidence and easy to manage. Conclusion: The encouraging results obtained with the FLN regimen in terms of clinical benefit and its predictable and manageable toxicity support the palliative role of this chemotherapeutic strategy in hormone-refractory prostate patients.*

Androgen-ablation therapy, either through bilateral orchiectomy or the administration of luteinizing hormone-releasing hormone agonists, associated or not with anti-androgens, has been a mainstay of treatment for advanced prostate cancer. Although most patients respond to androgen ablation as an initial systemic therapy, the median duration of response is no longer than 12-18 months (1). Nearly all patients will develop hormone-independent disease and, once the disease becomes hormone-refractory, the median survival ranges from 6 to 12 months (2). Anti-androgen withdrawal may induce a brief clinical response in about 30% of patients (3), but there is no consensus regarding the most appropriate second-line treatment to be given in patients with "hormone-refractory" disease. Despite the "recognized poor chemo-sensitivity" of prostate cancer, a number of single agents have been identified that have potential benefit in men with metastatic hormone-refractory disease.

Various single drugs such, as antimetabolities, alkylating agents, vinca alkaloids, nitrosoureas and combinations of drugs have shown little or no activity in inducing tumor regression, a drop of serum prostate specific antigen (PSA) levels and reduction of the pain score, but have failed to have a significant impact on survival. Recent studies demonstrated an impact on overall survival in patients treated with docetaxel (4, 5).

The response to chemotherapy treatment is conventionally measured by changes in the size of measurable bi-dimensional soft tissue lesions. Such lesions occur infrequently in patients with metastatic prostate cancer because of bone-only disease and, therefore, the conventional criteria for tumor response are not useful for phase II studies in this setting of patients. The change in the PSA level as a measure of response to chemotherapy is controversial, but has been used as a surrogate marker of response (6, 7).

In a population of elderly patients, symptom palliation should be the primary end-point of therapy with the aim of delaying the onset and/or progression of symptoms. Recently, studies emphasizing the "clinical benefit" as a principal end-point of antitumor treatment in advanced prostate cancer

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have shown that chemotherapy can result in an improved quality of life in advanced prostate cancer (7, 8).

Vinorelbine is a semi-synthetic vinca alkaloid that has a cytotoxic effect on a wide range of tumor cell lines (9). It is a mitotic inhibitor with a higher therapeutic index and less neurotoxicity than other vinca alkaloids, related to the lower degree of damage to axonal microtubules (10). The dose-limiting toxicity of vinorelbine is granulocytopenia (11).

The experience in prostate cancer with Vinorelbine is limited. Several phase II studies have shown promising results in terms of clinical response and reduction of analgesic consumption in patients with hormone-independent disease. These trials have demonstrated clinical benefit responses of 20-40% and 20% PSA-value reduction when used as single agent (12-16). The impressive effectiveness observed with Vinorelbine as a single agent and its favorable toxicity profile has led to its testing in combination with other cytotoxics in advanced prostate cancer.

The combination with other vinca alkaloids, etoposide and/or estramustine was shown to yield remissions in about 30-40%, with prolonged stable disease and manageable toxicity (17-19). 5-Fluorouracil in patients with hormone-independent disease, modulated by folinic acid or combined with cisplatin or interferons, also demonstrated clinical activity with a relativly good tolerability (20-22).

The results of a combination of Vinorelbine with 5-Fluorouracil (5-FU) and folinic acid (FA) (FLN regimen) were evaluated in 34 patients with progressive hormone-refractory prostate cancer (HRPC).

Patients and Methods

Patients. Patients were eligible if they had histologically-confirmed adenocarcinoma of the prostate, age <80 years, ECOG performance status (PS) ≤3, adequate bone marrow reserve defined by granulocyte count ≥1,500 x 10^9/l, hemoglobin >9.0 mg/dl, platelet count >100x10^9/l, adequate hepatic (bilirubin ≤2.0 mg/dl, AST≤3 the upper limit of normal except for liver involvement) and normal renal function (creatinine within the normal ranges) and an estimated life expectancy ≥12 weeks.

Patients with central nervous system involvement, peripheral neuropathy or unstable conditions, such as cardiovascular disease (myocardial infarction or active angina within 12 months before the study entry) were excluded.

Pain had to be stable during the last week before study entry. Patients with measurable or unmeasurable disease were included in the study. Informed consent was obtained before entry.

Pre-treatment evaluation and follow-up studies. Pre-treatment evaluation included a complete medical history, clinical examination, blood cell count, serum biochemistry profile, serum PSA, ECG, chest X-ray, computerized tomography of the abdomen and pelvis, radionuclide bone scan and X-ray details of pathological spots. Clinical monitoring was performed once weekly with a complete blood count.

Serum chemistries and serum PSA measurements were assessed every cycle. In patients with measurable disease, antitumor activity was evaluated every three courses (*i.e.*, 9 weeks) on all measurable sites and all of the patients were scheduled for at least two cycles in order to be eligible for assessment of tumor response. In patients with tumor responses or stable disease, the treatment was continued to a maximum of 8 cycles. In the event of suspicious progressive disease, due to a deterioration of the PS or a significant increase in values of PSA, disease sites were evaluated after two courses.

In patients with unmeasurable disease, treatment evaluation was performed with PSA monitoring at every cycle and with bone scan at the end of the sixth course.

Toxicity was graded according to NCI-CTC criteria (23). Patients were considered evaluable for toxicity if they received at least one cycle of chemotherapy. The response to therapy was mainly assessed on serial measurements of serum PSA levels. For documenting PSA response, a decrease ≥50% of baseline values in two consecutive measurements at a 3-week interval was required; if the marker increased >50% in two consecutive assays, progressive status was defined. Patients without deterioration of performance status, who did not meet the PSA criteria for progression, were considered to have stable disease.

In patients with measurable disease, tumor response was defined according to the WHO criteria (24). A complete remission (CR) required the complete disappearance of all disease as observed on a CT scan. A partial remission (PR) denoted a greater than 50% reduction in the sum of the products of the greatest perpendicular diameters of all tumor nodules by CT scan. A reduction or a progression less than 25% was considered to be stable disease (SD).

In the case of bone metastases concomitant to measurable sites: PR or SD were reported if PR or SD in measurable lesions was associated with PR or SD in PSA levels without bone pain progression. Pain was treated according to the WHO guidelines (25). They represent a sequential guideline, based on a 3-step approach. In the first step, patients with slight pain receive NSAIDs as the main analgesics; in the second step, weak opioids are added, for moderate pain. If severe pain is still present, weak opioids are substituted with strong opioids, namely morphine. This approach appears able to control the vast majority of painful cancer-related conditions (26).

Bone pain was evaluated according to analgesic consumption. Patients were divided into three groups, depending on the kind of drug used. The first group included patients requiring NSAIDs for satisfactory pain control (*e.g.,* Visual Analog Scale-VAS less than 4); in the second group were included those patients requiring weak opioids, namely tramadol or codeine, while the third group was comprised of patients requiring strong opioids, namely oral or parenteral morphine, oral methadone or transdermal fentanyl. The percentage of patients at each step and of those switching from one step to another were also registered. This evaluation approach closely follows the WHO guidelines for cancer pain control (25).

The clinical benefit response was defined by continued improvement in one category from the baseline ECOG PS for a minimum of 8 weeks or reduction of NSAIDs or analgesic consumption by an inverse step approach.

Statistical analysis. The primary objective of this phase II study was the assessment of the clinical benefit; secondary end-points

were the evaluation of antitumor activity, measured as overall response rate, response duration, time to progression, overall survival and toxicity.

Time-to-event end-points were estimated using the method of Kaplan and Meier (27). The duration of response was measured from the first documentation of response to the date of disease progression, for responders only. Progression-free survival was measured from the first day of treatment to the date of disease progression or death, whichever occurred first, for all registered patients. The overall survival was measured from the first day of treatment to the date of death, for all included patients.

Simon's two-stage optimal design was used for patient accrual (28). The regimen would be considered promising if a clinical benefit was obtained in at least 30% of the patients, but would be regarded unworthy if a clinical benefit was measured in less than 10% of the patients. The first stage was planned to accrue ten patients, with a second stage accruing an additional 19 patients if at least one patient achieved a clinical benefit in the first stage. The treatment would be considered active if at least six out of 29 patients responded. This design yields a probability of, at most, 0.05 of accepting a treatment as active whose true response rate was less than 10%, and a probability of, at most, 0.2 of rejecting a treatment whose true response rate was more than 30%.

Treatment plan. The treatment consisted of a fixed dose of 100 mg/m^2 FA administered by injection into a running *i.v.* infusion of dextrose 5% or normal saline over a period of 10 min on days 1 to 3, followed by 5-FU at a dose of 350 mg/m^2 administered by means of a 15-min *i.v.* infusion on days 1, 2 and 3. Vinorelbine was administered at 20 mg/m^2 diluted with 75-125 ml of normal saline or dextrose 5%, and infused for 20 min on days 1 and 3. Dexametasone, 8 mg *i.v.* on days 1 and 3, and 4 mg *i.v.* on day 2, was used as prophylactic anti-emetic treatment combined with metoclopramide at 20 mg on days 1-3. The treatment was administered in an out-patient setting every 3 weeks. Patients on medical therapy with luteinizing hormone-releasing hormone analogs continued this treatment to maintain their serum testosterone within castration level. Other hormonal agents had to be discontinued for at least 1 month before treatment initiation to overcome withdrawal responses.

The toxicity of each cycle was recorded before the administration of the next one. Dose modifications were made according to the worst toxicity observed during the previous cycle. A decrease of 5-FU, FA and Vinorelbine to 75% of total dose was performed in the case of NCI Grade 3 or 4 stomatitis, neutropenia, thrombocytopenia, diarrhea or other Grade 3 major organ drug-related toxicity, after delaying the cycle until full recovery from stomatitis or diarrhea and recovery of blood counts to: neutrophils > 1.5 x 10^9/l and platelets > 100 x 10^9/l.

Radiotherapy was allowed when other parameters of disease were documented, except for the treated side. In case of concomitant radiotherapy, the dose of 5-FU and FA remained unchanged, while Vinorelbine was reduced to a total dose of 20 mg.

Results

Thirty-four patients were enrolled between December 1996 and March 2000 and 30 were evaluable for analysis. The patients' characteristics are summarized in Table I. The median age was 70 years, range 45 -77. The median time from the progression on primary hormone treatment to the start of chemotherapy was 15 months (range 2 - 120).

Table I. *Patient characteristics at study onset.*

No. of patients	30
Age, years	
median	70
range	45 - 77
ECOG performance status	
1	20
2	9
3	1
PSA (baseline value)	
median	210
range	0.1-4364
no. of patients with PSA value <10	2
Measurable disease	15
Unmeasurable disease (only bone)	15
No. of sites of metastatic disease	
1	15
≥2	15
Metastatic sites	
bone	29
lymph nodes	14
lung/liver	1/1
Prior surgery (prostatectomy)	3
Previous endocrine treatment	
BAT	30
others	9
Previous chemotherapy (types)	
estracyt	23
others	2
No. of medical treatments	
1 (BAT)	5
2	19
3	6
Concomitant treatments	
radiotherapy	
primary	1
bone lesions	3
endocrine treatment	30

A total of 127 treatment cycles (median 3, range 1-8) was administered. Treatment was discontinued before completing two cycles in four patients: one for sudden death without cardiac anamnesis, one for rapid deterioration of PS, one for duodenal perforation due to concomitant NSAIDs and one for cumulative toxicity due to concomitant radiotherapy and chemotherapy (protocol violation). In one patient the treatment was completed for all eight planned cycles. Ten cycles out of 127 (7.8 %) were delayed in six patients for hematological toxicity; six patients required a dose reduction in eleven cycles because of G3 neutropenia (3), G3 anemia (2) and moderate asthenia (1). Thus, 116 cycles (91%) were administered at full dose.

Table II. *Toxicity data for FLN regimen (NCI-CTC Grade). Number of patients: 30.*

	Grade			
Toxic event	1 No.	2 No.	3 No.	4 No.
Leukocytes	2	4	6	2
Neutropenia	1	0	3	5
Anemia	1	6	2	0
Thrombocytopenia	1	0	0	0
Hepatic AST	3	0	0	0
Hepatic ALT	2	0	0	0
Total bilirubin	0	0	0	0
Nausea/Vomiting	8	3	0	0
Diarrhea	3	0	0	0
Constipation	9	3	0	0
Mucositis	3	2	0	0
Alopecia	1	0	0	0
Asthenia	9	3	1	0

The most common toxicity was hematological with Grade 4 granulocytopenia observed at re-cycle of treatment in five patients. Symptomatic anemia requiring transfusions was reported in two cases. The worst grades of hematological toxicity in patients are summarized in Table II. The other toxicities were of low incidence and mild in severity (Table II). No severe nausea or vomiting was reported. No superficial phlebitis or deep venous thrombosis was described and, in this case, the possible protective role of the central-venous-catheter was considered.

Response. Out of the 15 patients with measurable disease, four partial responses (PR) (26.6%; 95% C.I., 28.3% to 65.7) were reported, three in the lymph nodes and one in the lung. In two patients with bone and soft tissue disease involvement, bone localization was evaluated with CT and bone scan that confirmed PR. In the remaining eleven patients, four stable disease (SD) and seven progression of disease (PD) were observed. Six out of 15 patients with only bone disease had SD and nine PD. Disease stabilization was obtained in ten patients out of the 30 evaluable cases (33%). The median duration of response and stabilization was 4 months (range 2-6). The median time to progression (TTP) and median overall survival time (OST) were calculated on all 34 registered cases (intention-to-treat analysis) and were of 10 (range 1 - 34+) and 42 weeks (range 1+ - 66+), respectively.

Six out of the 30 patients (20%) had a biological response with a serum PSA decline of >50% or more and eihgt cases (26.6%) presented PSA stabilization. Among four responders, two PSA reductions ≥50% and two PSA stabilizations were reported, while four PSA responses were observed in ten patients with SD. The biological response was correlated with clinical improvement in six patients. All 30 patients presented PS≥1 at baseline evaluation: PS improved in four cases with PR and in ten cases with SD (14 patients, 47%) , while it was unchanged in the 16 remaining patients. All 30 patients presented bone pain requiring analgesics at the onset of chemotherapy: 14 achieved a significant reduction of pain; in two cases pain remained stable, but worsened in the remaining 14. Among the 15 patients with NSAIDs, five were able to stop analgesic medications, five patients out of the ten treated with weak opioids switched to NSAIDs and, of the five patients who received strong opioids, four switched to weak opioids.

Discussion

The aim of this study was to evaluate the efficacy of a combination of Vinorelbine, 5-FU and FA, in patients with HRPC. A regimen with a low subjective toxic burden appeared attractive in elderly patients, preserving and, when possible, improving their quality of life. Based on the premise of an easy and manageable regimen for HPRC patients, with the aim of controlling tumor-related symptoms and increasing progression-free survival, we tested an experimental regimen that we had used in breast cancer (29). In detail, we had observed that Vinorelbine plus FA and 5-FU, in advanced breast cancer, had considerable efficacy (response rate 60% with CR 18%) with an excellent subjective tolerability: the dose-limiting toxicity was Grade 3-4 neutropenia recorded at nadir, with a very low incidence of Grade 2 nausea, vomiting and alopecia.

The clinical experience related to prostate malignancy indicates the difficulty in documenting responses to systemic therapies according to traditional criteria, owing to the preponderance of patients with only bone metastases (non-measurable disease). Different criteria have to be considered to evaluate the clinical response as a clinical benefit index: namely amelioration of the PS, subjective reduction of cancer pain and reduction of analgesic intake.

The role of the PSA test in HRPC is unclear, even if it remains a highly sensitive tumor marker for screening, for monitoring loco-regional spread after medical or surgical treatment, for evaluating residual disease or for early detection of tumor relapse (30, 31). There are some data supporting the evaluation of PSA values as a surrogate response parameter, although it is known that tumor progression may occur in a subset of patients even without concomitant increased PSA levels (32). The results of our study confirmed the role of chemotherapy as a palliative treatment for HRPC. The overall data regarding median TTP or median overall survival are similar to those obtained by most mono- and poly-chemotherapy associations with the

advantages of good patient tolerance and mild and reversible toxicity. Specifically, recent data on docetaxel activity in HRPC showed a 45% and 48% reduction in PSA levels in patients receiving docetaxel weekly and every 3 weeks, respectively. All these patients received high-dose dexamethasone due to docetaxel premedication. Our patients received a low dose of steroids.

Previous studies conducted with Vinorelbine, used as a single agent or in combination, reported similar results in terms of clinical impact and patient benefit. In our series, no local reaction or superficial or deep venous thrombosis was witnessed, thereby contributing to a better compliance to the treatment plan. No paresthesias, constipation or other neurological side-effects attributed to the vinca alkaloids were registered. The amelioration of the PS in symptomatic patients was detected in 14 (47%) patients.

Our data, compared to the results regarding mitoxantrone and prednisone described by Tannock *et al.* in a randomized trial, showed a more consistent improvement in pain control and/or a decrease in analgesia associated with improvements in the PS, a minor duration of response, probably due to unfavorable patient characteristics, but a similar overall survival time (7, 33).

In 46.6% of the patients, a significant reduction and stabilization of the PSA were reported and, in six of these patients, the PSA values were reduced by 50% or more with respect to the baseline documentation. We observed a correlation between the PSA measurements and clinical outcome in the majority of patients in our series. The decrease in serum PSA levels was not always consistent with clinical response to treatment and in only six out of 14 cases showing clinical benefit was a biological correlation found. This discordance had been observed in other studies of patients with prostate cancer (17, 34-36). Thus, the role of this marker remains unclear in this population of patients.

The manageable and predictable toxicity of the regimen investigated here was associated with encouraging results related to clinical benefit. We can conclude that chemotherapy (FLN regimen) is a reasonable option in patients with HRPC for its palliative role in cancer pain, however, the optimal timing of its use has to be explored.

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