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European Journal of Cancer 38 (2002) 1626–1632

European Journal of Cancer

www.ejconline.com

Vinorelbine in androgen-independent metastatic prostatic carcinoma—a phase II study

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Received 18 December 2001; received in revised form 14 March 2002; accepted 3 May 2002

Abstract

The purpose of this study was to evaluate the efficacy of vinorelbine treatment in terms of prostate-specific antigen (PSA) response and clinical benefit (decrease of pain or analgesic score for the subgroup of patients with pain), as well as its toxicity in patients with progressive metastatic androgen-independent prostatic carcinoma. 44 patients with prostatic carcinoma progressing after orchiectomy or during treatment with hormonal agents were treated with vinorelbine at a dose of 30 mg/m^2 intravenously (i.v.) on days 1 and 8 of a 21-day cycle. Inclusion criteria were metastatic progressive prostatic carcinoma with prostate-specific antigen (PSA) serum levels $\geqslant 3\times$ upper limit of normal, World Health Organization (WHO) performance status $\leqslant 2$, age <85 years and adequate bone marrow, liver and renal functions. Treatment was continued until progression or a maximum of 12 cycles. Treatment was delayed for a week if haematological toxicity grade $\geqslant 2$ was observed on the day of scheduled vinorelbine administration. 9 patients received less than three cycles, 6 due to rapid tumour progression. Treatment at day 1 had to be delayed in 13.7% of 183 cycles. Treatment at day 8 had to be omitted in 19.7% of all cycles. Grade $\geqslant 3$ granulocytopenia occurred in 18% of patients. 4 patients had severe constipation. In 7 patients (15.9%, Confidence Interval (CI) 6.6–30.1%), a PSA response ($\geqslant 50\%$ reduction of PSA levels) was observed. Among 8 patients with measurable disease, 3 had partial remission and 1 no change. Median time to PSA progression in 43 assessable patients was 11.9 weeks (range 3–52 weeks). Median duration of PSA response was 14 weeks (9–30 weeks). Clinical benefit was seen in 7 of 31 cases (23%) with baseline pain, there was no association with PSA response. Vinorelbine is a fairly well tolerated drug with a moderate single agent activity in patients with androgen-refractory prostate cancer.

Keywords: Prostatic carcinoma; Hormone resistance; Vinorelbine; Prostate-specific antigen (PSA); Quality of life; Clinical benefit

1. Introduction

Despite recent medical advances, the median survival of patients with metastatic hormone-refractory prostate cancer (HRPC) is only between 9 and 12 months [1,2]. Second-line hormonal manipulations after medical or surgical castration may result in repeated tumour responses [3] and various new drugs and combination regimens have been introduced into the clinic, although with still limited efficacy. Chemotherapy in patients with HRPC has been shown to decrease serum levels of prostate-specific antigen (PSA), to shrink soft-tissue metastases, to improve bone scans and, most importantly, to improve aspects of quality of life (QL), especially with regard to pain [4.5]. However, a prolongation of survival following chemotherapy treatment has not been observed in the four existing phase III trials [4]. Further studies with more efficacious drugs and more effective combinations are therefore needed. Interpretation of existing phase II studies of cytotoxic drugs is complicated for a variety of reasons. There are differences in the patient characteristics concerning age, general health status, socioeconomic factors and extent of

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0959-8049/02/$ - see front matter
PII: S0959-8049(02)00145-4

disease. Furthermore, outcome has often been reported using different criteria.

Starting in 1991, the Swiss Group for Clinical Cancer Research (SAKK) has conducted three consecutive phase II trials within the framework of a master protocol to evaluate carboplatin [6], idarubicin [7] and gemcitabine [5] in patients with HRPC. The goal of such studies was to find promising new drugs for further testing in phase III trials. These multicentre phase II studies included similar, but evolving requirements with respect to the documentation of response, toxicity, quality of life and serial PSA measurements. The fourth drug to be tested was vinorelbine. Preliminary results of this trial were presented in abstract form [8].

Vinorelbine (Navelbine®, Robapharm, Switzerland) is a semi-synthetic vinca-alkaloid, which reversibly binds to tubulin resulting in mitotic cell spindle dissolution and metaphase arrest. It has shown encouraging results in many solid tumours, such as breast cancer and non-small cell lung cancer [9]. Compared with other vinca-alkaloids (vinblastine, vincristine, vindesine), it is less active on axonal microtubules, suggesting a potential for less neurotoxicity.

The objective of the present trial was to evaluate the efficacy of vinorelbine in terms of PSA response and clinical benefit, and its toxicity. The primary endpoint of the study was PSA response [10,11] according to the recently published guidelines [12]. In the subset of patients with measurable disease, response was documented according to classical World Health Organization (WHO) criteria.

2. Patients and methods

Between October 1997 and September 1999, 44 patients with HRPC were enrolled. The trial was designed as a classical two-stage phase II study. If no PSA responses were observed in the first 14 patients, the accrual was to be stopped; otherwise recruitment to the second stage would continue up to a total of at least 40 patients. All patients had progressive disease (rising PSA levels and/or new or growing metastases) diagnosed while on continued androgen ablation: 31 had a bilateral orchiectomy, 13 received a luteinising hormone-releasing hormone (LH-RH) agonist, which had been stopped in 2 cases after PSA progression before enrolment on the study. A total of 23 patients had been treated during the course of their disease with an androgen receptor blocker either concomitantly or as a second-line hormonal therapy. However, treatment with anti-androgens had to be stopped at least one month before study enrollment so that an anti-androgen withdrawal response [13] was not falsely attributed to the study drug. Palliative radiation therapy was not allowed within one month prior to chemotherapy and irradiated metastases were not to be used for the response evaluation.

All patients had to have pathologically documented metastatic prostatic carcinoma and had to have failed prior androgen ablation. Eligibility criteria included an upper age limit of 85 years, a life expectancy of more than 12 weeks, a WHO performance status of 0–2 and the absence of known leptomeningeal or brain metastases. No previous cytotoxic therapy, including estramustine, was allowed. Requirements for laboratory values included a serum PSA of at least three times the upper normal level; leucocytes (WBC) $\geqslant 3.5\times10^9$/l or granulocytes $\geqslant 2\times10^9$/l, platelets $\geqslant 100\times10^9$/l, haemoglobin $\geqslant 90$ g/l, serum creatinine $\leqslant 1.5\times$upper normal value, bilirubin $\leqslant 1.5\times$upper normal level, and asparate aminotransferase (SGOT) $\leqslant 2.5\times$upper normal level. Measurable and non-measurable metastatic disease was allowed. Bone metastases alone were considered to be non-measurable. The trial had been approved by the scientific committee of the SAKK, by the local ethical committees of the participating institutions, and written informed consent was obtained from each patient before entering them on to the trial.

Vinorelbine (Navelbine®) was provided free of charge by Robapharm Switzerland (Pierre-Favre) and was administered at a dose of 30 mg/m^2 (maximum dose 60 mg) by rapid intravenous (i.v.) infusion of 5–10 min duration on days 1 and 8 of each 21-day cycle. Treatment was continued for a minimum of three cycles up to 12 cycles, unless the patient refused treatment, there was unacceptable toxicity or tumour progression occurred (new lesions, increase of measurable lesions or PSA progression). Chemotherapy was delayed for a week if haematological or neurological toxicity grade $\geqslant 2$, or hepatic toxicity grade $\geqslant 3$ were observed on the day of scheduled vinorelbine administration. No dose reductions were foreseen in the protocol. The patients were to be followed until disease progression.

Evaluation at the start of each treatment cycle included medical history, a physical examination, complete blood count, serum chemistry, measurement of PSA and a pain/quality of life assessment. Radiological examinations consisted of a bone scan and selected bone X-rays, chest X-ray and a baseline computed tomography scan of the abdomen. Electrocardiography was required at study entry.

In the protocol, PSA responses were defined as CR (complete response of PSA), PR (partial response) or NC (no change). For the final analysis, these criteria were replaced by the recently published guidelines for phase II trials in HRPC [12]. A PSA response was defined as a decrease of serum PSA levels by at least 50% compared with baseline and had to be confirmed by a second determination after four weeks. Moreover, no increase in the size of pre-existing metastases, no appearance of new lesions and no clinical signs of tumour progression were allowed. Progression (PD) was defined as a confirmed increase of PSA values by at least 25% compared with baseline or nadir. Duration of the

PSA response was measured from the time at which PSA had declined to $\leqslant 50\%$ to the time when PSA had risen by 50% above the nadir. Toxicity was assessed according to WHO criteria.

Pain treatment was not standardised, but recorded and classified by the treating physician at registration, on day 8, at the start of each treatment cycle and at treatment failure. A pain treatment score was calculated according to Moore and colleagues [14] for each visit by an independent physician. The use of standard tablets or capsules of non-narcotic analgesics were assigned 1 point each; standard doses of narcotic analgesics were assigned 2 points (e.g. hydromorphone 2 mg, morphine 5 mg, etc.). These points were totalled for a daily score and averaged into a score assessing the week before the clinical visit.

Quality of Life (QL) was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30) [15] at registration, on day 8, at monthly visits and at treatment failure. All scales and single-items were transformed according to EORTC guidelines to a range from 0 to 100. A higher score for a functional scale represents a higher level of functioning, a higher score for the global health status/QL scale a better QL, and a higher score for a symptom scale or item a higher level of symptoms or problems. In addition, a global indicator for overall treatment burden [16] and another for coping effort [17] were included. These two indicators were transformed accordingly (0–100), with higher scores indicating better QL. All questions referred to experience during the previous week. Pain (QLQ-C30: items 9 + 19), was prospectively defined as the primary QL endpoint, the other measures were used for descriptive purposes only.

Palliative benefit in terms of reduction in patient-rated pain and/or use of analgesics was defined as follows: From baseline, for at least two consecutive cycles (i.e. 6 weeks), either a decrease of $\geqslant 2$ response categories (corresponding to $\geqslant 33\%$) in the pain scale (items 9 + 19) without an increase in analgesics, or a decrease by $\geqslant 50\%$ in analgesics without an increase in pain, was required.

For the minority of patients who did not report pain at baseline, we prospectively defined changes in physical functioning and global health/quality of life (both from QLQ-C30) as benefit criterion as follows: From baseline, for at least two consecutive cycles (i.e. 6 weeks), either an improvement of $\geqslant 2$ response categories (corresponding to $\geqslant 40\%$) in physical functioning without any worsening in global health status/QL, or an improvement of $\geqslant 3$ response categories (corresponding to $\geqslant 25\%$) in global health status/QL without any worsening in physical functioning, was required.

We investigated changes in QL measures from baseline to subsequent timepoints. Changes which were present in means, but not in medians (i.e. median = 0) were not considered relevant. Although the transformation of the QLQ-C30 scales results in scores ranging from 0 to 100, these measures are still categorical in nature. In small samples as the present one, effects should be reflected in the medians as well, otherwise they are probably not relevant. The impact of PSA response and clinical benefit (i.e. cases with baseline pain) on the QL measures was investigated as the change from baseline according to the definitions described above. Given the small number of cases with PSA response or benefit, the impact of time from registration, PSA response and benefit was explored in longitudinal analyses (i.e. linear mixed models) using all available measurements before treatment failure with baseline scores as covariates. All tests were two-sided. No adjustment was made for multiple testing.

3. Results

The 44 men entered on the study had a median age of 71 years (range: 45–83 years) and were in good general health with 36 of 44 patients having a performance status of 0 or 1 (see Table 1, patient characteristics). In 70% of the patients previous androgen ablation was by means of an orchiectomy (31 of 44 patients). Approximately half of the patients (23 of 44) had undergone previous radiation therapy.

In 2 patients, no demonstrable tumour metastases were documented, contrary to the inclusion criteria and for 1 patient no documentation of a PSA progression prior to study entry was obtained. In 3 patients, haematological values at start of the study did not fulfil the entry requirements (haemoglobin levels of 89 and 81 g/l, respectively, WBC of 3.3×10^9/l and 3.1×10^9/l) and in 1 patient each, SGOT was 3.7 ULN (up to 2.5 ULN was allowed) and creatinine 1.7 ULN (up to 1.5 ULN was allowed). Following the intention-to-treat principle, all of these patients were included in the analysis.

A total of 183 chemotherapy cycles were administered with a median of four cycles and a range of 1–9 cycles per patient. Delay of the day 1 dose was reported in 25 cycles (13.7%), 17 times due to low haematological parameters. The day 8 administration was cancelled in 36 cycles (19.7%), 20 times due to low haematological values. The median dose per administration was 55 mg. Dose reductions were not foreseen in the protocol but were documented in 18 cycles. In five cycles granulocyte-colony-stimulating factor (G-CSF) was added.

Toxicity (grade $\geqslant 2$) is reported in Table 2. The main toxicity was haematological, with limited periods of granulocytopenia. 16 serious adverse events were reported, including 3 cases of febrile neutropenia, which were all resolved. Other serious adverse events were due to tumour progression or concomitant morbidity leading

Table 1
Patient characteristics ($n = 44$)

Category	Frequency (%)
Performance status (WHO)	
0	10 (23)
1	26 (59)
2	8 (18)
Previous radiotherapy	
No	21 (48)
Yes	23 (52)
Orchiectomy	
No	13 (30)
Yes	31 (70)
LH-RH analogues	
No	31 (70)
Yes	13 (30)
Anti-androgens	
No	20 (45)
Yes	24 (55)
Measurable disease	
No	36 (82)
Yes	8 (18)
Tumour localisation[a]	
Bone	38 (86)
Lymph nodes	11 (25)
Lung	4 (9)
Pleura	4 (9)
Liver	5 (11)
Others[b]	2 (5)
	Median (range)
Age (years)	71 (45–83)
Weight (kg)	76.5 (57–104)
Disease duration since diagnosis (years)	2.8 (0.3–12.9)
PSA (ug/l)	237.5 (17.1–7178)
Alkaline phosphatase × ULN	1.5 (0.3–10.6)

PSA, prostate-specific antigen; LH-RH, luteinising hormone-releasing hormone; WHO, World Health Organization; ULN, upper limit of normal.

[a] Each patient may have more than one tumour localisation.

[b] Chest wall and peritoneal.

Table 2
Toxicity WHO grade 2–4

Toxicity	Grade	No of cycles 183	No. of patients 44 patients (%)
		Cycles (%)	
Anaemia	2	44 (24.0)	18 (41)
	3	8 (4.4)	5 (11)
	4	0	0
Leucopenia	2	34 (18.6)	10 (23)
	3	21 (11.5)	16 (36)
	4	0	0
Granulocytopenia	2	14 (7.7)	3 (7)
	3	11 (6.0)	5 (9)
	4	7 (3.8)	4 (9)
Thrombocytopenia	2	3 (1.6)	1 (2)
	3, 4	0	0
Phlebitis	Yes	6 (3.3)	3 (7)
Constipation	2	17 (9.3)	5 (11)
	3	4 (2.2)	4 (9)
Neurological	2	1 (0.5)	1 (2)
	3	2 (1.1)	1 (2)
Nausea/vomiting	2	9 (4.9)	7 (16)
	3	1 (0.5)	1 (2)

WHO, World Health Organization.

to exacerbation of pain, fracture of the femoral neck in 2 cases, and 1 event of seizures, cholecystitis and perforated diverticuli, respectively. In 2 cases, severe constipation was reported. This was judged to be a consequence of treatment or at least to be exacerbated by the study drug.

All patients except 1, were followed until disease progression. 9 patients had early treatment failure (i.e. <3 treatment cycles): 6 cases due to early disease progression, 2 serious adverse events were due to constipation in 1 patient and neurological toxicity with depression and general weakness in another, and 1 patient refused further treatment. In the remaining 35 patients, treatment was stopped due to tumour progression in 26 cases, due to adverse events in 2 cases (angina pectoris, hip fracture) and in 7 cases for other reasons including refusal in 5 patients.

In 7 patients, a $\geqslant 50\%$ confirmed decline of PSA values was documented, resulting in a PSA response rate of 15.9% (95% Confidence Interval (CI) 6.6–30.1%). 4 of these patients had a PSA reduction by $\geqslant 75\%$ and one by $\geqslant 90\%$. 5 additional patients had for one measurement a PSA reduction by $\geqslant 50\%$, which was, however, not confirmed in 3 cases or did not qualify as a PSA response due to clinical progression in 2 patients. The PSA profiles are shown in Fig. 1.

For comparative purposes, we evaluated PSA response also according to the criteria specified in the trial protocol. After exclusion of 9 patients receiving less than three cycles and considered non-evaluable, there was 1 patient with a CR (3%), 6 with a PR (17%) and 17 with NC (49%). This adds up to 20% the patients experiencing CR + PR or 69% experiencing CR + PR + NC. The 7 responders were identical with those who had a PSA response according to the recent guidelines. Concerning the response in measurable disease, in 3 of 8 patients tumour responses were documented; in the lung (2 patients) and lymph node metastases (1 patient).

In 1 patient, the PSA response could not be determined due to missing values. Among the 43 assessable patients, 29 had rising PSA levels on treatment. In 11 patients, disease progression occurred after discontinuation of the trial treatment. The interval between follow-up visits was 3 months, which was much longer than the 3-week interval during treatment. Therefore, the dates of PSA and clinical progression of these patients were considered

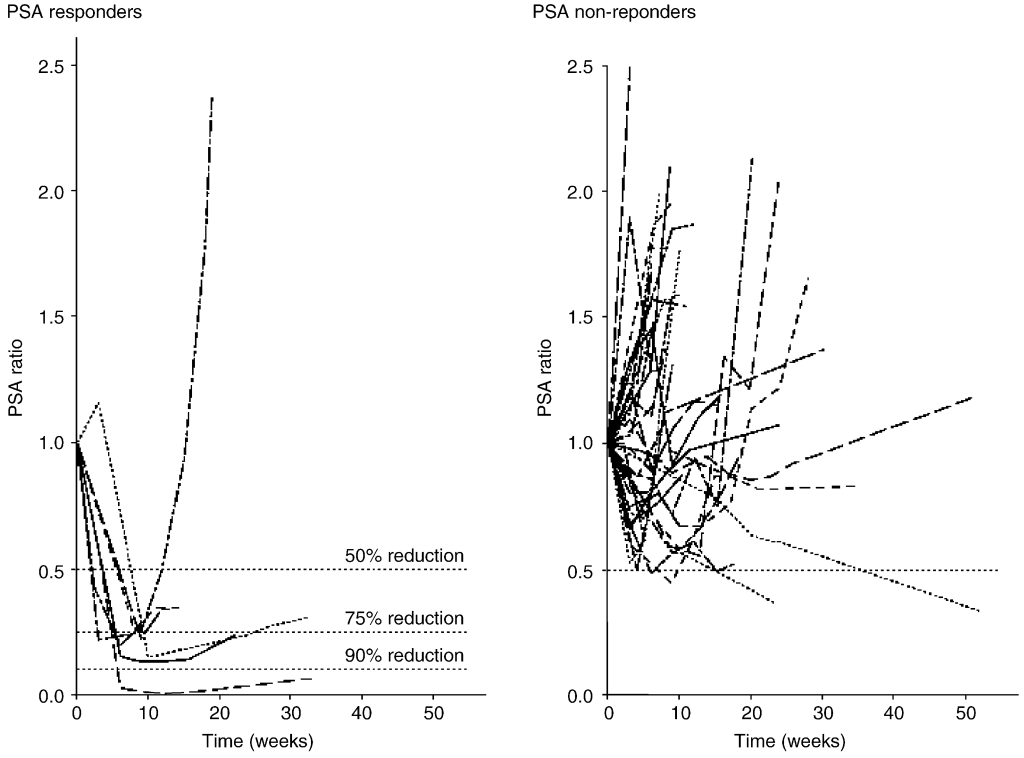

Fig. 1. Prostate-specific antigen (PSA) ratio relative to baseline for PSA responders and non-responders. Stabilisation of PSA levels can also be seen in some patients considered non-responders.

interval censored in the interval between the previous visit and the last follow-up visit.

The median time to PSA progression was 11.9 weeks with a range of 3–52 weeks (Fig. 2). Median duration of PSA control in all assessable 43 patients was 6 weeks (3–30 weeks). Median duration of PSA response of the 7 responders was 14 weeks (9–30 weeks). The resulting median time to PSA or clinical progression in all 44 patients was 10.4 weeks (3–52 weeks) (Fig. 2).

Of all 239 of the expected QL forms, 229 (88%) were received and correctly timed, 43 (98%) at baseline, 154 (90%) under treatment and 32 (73%) at treatment failure. QL forms were missing due to local administrative failure (43%), treatment-related toxicity (30%) and patient refusal (27%). Prefailure QL data were evaluated up to and including cycle 5 because too few patients were left on the trial treatment.

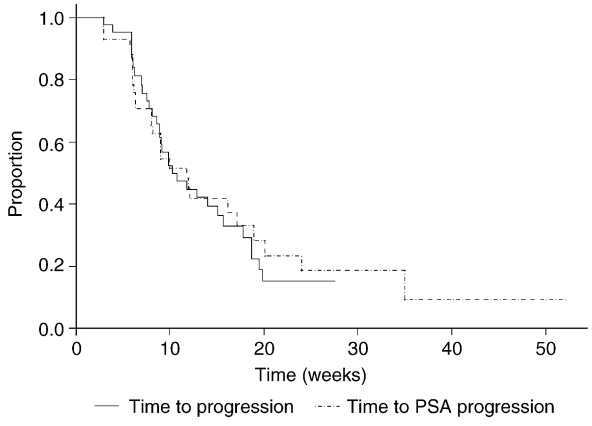

Fig. 2. Time to first progression (prostate-specific antigen (PSA) or clinical) and time to PSA progression.

At baseline, patients indicated a considerably impaired health status/QL ($n=42$, median = 54.2) and high treatment burden scores ($n=43$, median = 50). Fatigue ($n=43$, median = 44) was the most pronounced symptom of the QLQ-C30, followed by pain, dyspnoea, insomnia and appetite loss (all $n=43$, median = 33.3).

At day 8 of the first vinorelbine cycle, there was no worsening of short-term side-effects in any of the QL measures. Over the first five cycles, overall, there was no substantial change. Fatigue showed a tendency to worsen.

At treatment failure, role ($n=32$, median change = −16.7) and emotional ($n=32$, median change = −8.3) functioning, fatigue ($n=32$, median change = 11.1), health status/QL ($n=31$, median change = −8.3) and coping ($n=32$, median change = −8.3) showed the expected deterioration.

In agreement with patient-rated pain, physician-rated pain remained stable over time (baseline: $n=44$, median = 1). The pain treatment score indicated a stable consumption of analgesics (baseline: $n=44$, median = 1.8).

31 patients reported baseline pain. 7 of these cases (23%) met our criterion for clinical benefit from the investigated chemotherapy. For at least two consecutive

cycles, these patients indicated either a decrease of $\geqslant 2$ response categories in the pain scale from baseline without an increase in analgesics, or a decrease by $\geqslant 50\%$ in analgesics without an increase in pain. Only 1 of them also had a PSA response. There was no consistent impact of either PSA response or benefit on any of the QL measures (data not shown).

12 patients indicated no baseline pain. Their physical functioning and global health/QL were almost stable and did not suggest a benefit from vinorelbine treatment according to our criterion.

4. Discussion

Previous studies have shown that cytostatic therapy in patients with HRPC can lower PSA levels, shrink soft-tissue metastases and, most important of all, improve quality of life, and, in particular, can palliate pain.

The PSA response rate in this trial was 15.9%. Median duration of PSA response in the 7 responders was 14 weeks (9–30 weeks). Median time to PSA progression was 11.9 weeks (3–52 weeks). Median duration of PSA control was 6 weeks (3–30 weeks). Median time to either PSA or clinical progression was 10.4 weeks (3–52 weeks). In 6 cases, PSA progression was not present at the clinical progression. Irrespective of the applied response definition, the response rates obtained in this trial are higher than in our previous trials [5–7] and vinorelbine was the most active single drug examined.

Our results can be compared with two similar phase II trials with overlapping CIs of PSA response. Fields-Jones [18] could demonstrate a PSA response in only 4 of 49 (8%) patients. Oudard and colleagues [19] reported a PSA response in 6 of 47 patients (6 of 36 evaluable patients, 17%). In a previous abstract from the same study, Caty and colleagues [20] had reported PSA responses in 19 of 47 (40%) patients, apparently according to less stringent criteria. These various findings highlight the importance of using identical response criteria.

Vinorelbine has also been tested in the combination with estramustine. Carles and colleagues [21] reported PSA response in 9 of 24 (38%) patients but no measurable response in 5 patients with measurable metastases. Smith and colleagues [22] found in 6 of 25 (24%) patients a PSA response, with a median response duration of 10 weeks (3–39 weeks), but no objective response of measurable metastases. A combination of estramustine, oral etoposide and vinorelbine achieved a PSA response rate in 8 of 25 patients (32%), in a study described by Colleoni [23].

Using the criteria defined for pancreatic cancer [24], Fields-Jones and colleagues reported a clinical benefit in 14 of 37 (39%) evaluable patients treated in a similar manner to our patients. This is a noticeably higher percentage than the 7 of 31 cases (23%) with baseline pain in our trial. Oudard and colleagues [19] reported a clinical benefit in 15 of 21 (71%) assessable patients, or 32% of all patients, but used different criteria, including also patients with a stable pain score and performance status.

In our trial, in only 1 of the patients with clinical benefit could a concomitant PSA response be seen. Neither PSA response nor benefit had an impact on the QL measures. This discrepancy between clinical or PSA responses and pain response has also been observed by others. For example, Dowling and colleagues [25] noticed in a further analysis of their randomised trial [4] a relatively weak, although statistically significant, association between PSA response and palliative response. Of 45 patients with a palliative response, 19 (42%) had a PSA response, but 8 (18%) had rising PSA levels. In our previous trial with gemcitabine [5], clinical benefit was also documented in 5 of 43 (12%) patients who had progression of disease by PSA response. In an earlier SAKK trial [6] using carboplatin, 7 of 27 (26%) patients had an improvement of pain or decrease of analgesic consumption with no clear-cut association between clinical and PSA response. It is likely that the mechanism of palliation is different to the pathways leading to PSA responses. Palliation of pain might occur, for example, by modifying the activity of inflammatory cells or changing the secretion of mediators of inflammation and pain, independent of any tumoricidal effect or effect on PSA secretion.

Overall, the QL data indicate that vinorelbine was relatively well tolerated. In particular, there was no worsening of QL in short-term toxicity measurements. Only 3 cases of treatment failure were due to toxicity. However, there was no overall improvement in patient- or physician-rated pain. This is an indication of limited palliation and differs from results in our previous trials [5–7]. Similarly, the QL measures did not suggest an improvement whilst undergoing treatment. At treatment failure, these measures showed the expected worsening, supporting their clinical validity.

In conclusion, vinorelbine was fairly well tolerated in our patients and had demonstrable effects, i.e. shrinkage of soft-tissue metastases and a lowering of PSA levels. However, there was only a modest overall palliative effect. During the last decade drugs acting on tubulin and the cell spindle have shown impressive activity in patients with advanced prostate cancer. Currently, a company-sponsored international phase III trial comparing the combination of vinorelbine and estramustine to single drug estramustine is underway. Future developments include the oral form of navelbine.

Acknowledgements

The study was supported in part from a grant of Robapharm, Switzerland.

Appendix. Participating institutions and investigators

Kantonsspital St. Gallen (D. Ackermann, R. Morant, B. Thürlimann), Inselspital Bern (M. Borner), Kantonsspital Aarau (M. Wernli), Kantonsspital and private practice Chur (F. Egli, P. Forrer), Hospital and private practice Baden (F. Kocher, A. Streit), Hospital Olten (M. Rabaglio) Hospital Ilanz (D. Bernasch), Hospital Thun (J. Lüthi), Universitätsspital Zürich (E. Jacky), CHUV Lausanne (J. Bauer).

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