Response and palliation in a phase II trial of gemcitabine in hormone-refractory metastatic prostatic carcinoma


*See pages 187–188 for a list of participating institutions and investigators

Summary

Background: In a phase II trial, 43 patients with hormone-refractory prostate cancer were treated with gemcitabine at a dose of 1200 mg/m² over 2 hours (later decreased to 1000 mg/m² due to hematological toxicity) on days 1, 8 and 15 of a 28 day cycle.

Patients and methods: Inclusion criteria were proven tumor progression after hormonal treatment and increased PSA levels, a WHO PS ≤2, adequate bone marrow reserve, liver and renal function and age ≤80 years. Response criteria were based on PSA levels (CR: normalization of PSA, PR: > 50% decrease). Quality of life (QL) was assessed with the EORTC QLQ-C30 on day 1 of each treatment cycle and on day 8 of the first cycle (range of scales 0–100). Physician-rated pain intensity and use of pain medication were assessed at the same timepoints.

Results: Hematological toxicity of gemcitabine led to a dose-reduction in 48% of all cycles. Three of forty-three patients (RR = 7%) showed a PSA response: one CR and three PR with time to treatment failure of 8.7, 6.6 and > 9.3 months. Seven patients (16%) had stable disease (NC) for a median duration of 7.1 months (range 6.1–11.7 months). There was one case with objective regression of lymph node metastases. Patients reported a considerably impaired health status/QL (n = 41, median = 50) and severe fatigue (n = 41, median = 55.6) at baseline, with no change under treatment. Pain (QLQ-C30) was also severe at baseline (N=41, median=50) but was improved at the end of cycles 1 (n = 33, median change = -16.7, P = 0.0002), 2 (n = 19, median change = -33.3, P = 0.0006), 3 (n = 14, median change = -16.7, P = 0.06) and 4 (n = 9, median change = -33.3, P = 0.04). Patient-rated pain and use of analgesics as combined endpoint yielded palliation for at least 8 weeks in 14 patients (32%). Nine of these patients showed at least stable disease (CR/PR or NC by PSA level), five indicated a benefit in spite of progressive disease.

Conclusions: Gemcitabine in the dose and schedule indicated above has a significant beneficial impact on pain in patients with hormone-refractory prostatic carcinoma despite its limited activity in terms of PSA response and considerable, especially hematological, toxicity.

Key words: gemcitabine, gormone-refractory prostate cancer, pain, palliative endpoints, prostate specific antigen, quality of life

Introduction

The treatment of hormone-refractory advanced prostate cancer remains a clinical challenge [1]. There is no generally accepted cytostatic standard therapy after failure of hormonal treatment. Various single drugs or combinations have been shown to induce tumor regression, a drop of serum prostate specific antigen (PSA) levels and a reduction of pain scores but not yet a prolongation of survival. Combinations of drugs interacting with microtubuli, such as estramustine either with vinblastine, paclitaxel or etoposide, have been shown to induce PSA remissions in 30%–60% of patients [2–4].

Conventional criteria of tumor remission are not useful for phase II studies in this patient population because about 2/3 of the patients have metastases restricted to bone, considered to be non-measurable. PSA response has therefore been used as a surrogate marker of response [5–7]. Various study groups have emphasized quality of life (QL) endpoints in such studies [8–12]. 'Clinical benefit' of anti-tumor treatment has been defined by changes in pain and use of pain medications. In a randomized trial, Tannock et al. [12] have shown that the combination of mitoxantrone and prednisone has superior palliative response compared to prednisone alone.

The Swiss Group for Clinical Cancer Research (SAKK) conducted a clinical trial of gemcitabine (deoxy-defluorocytidine monohydrochlorid) within a master protocol for consecutive phase II studies in patients with hormone-refractory advanced prostate cancer [13, 14]. Gemcitabine is an antimetabolite with proven activity in various solid tumors such as pancreatic carcinoma, lung cancer and ovarian carcinoma. Based
on clinical benefit in a randomized clinical trial, Gemcitabine was introduced into clinical practice for the treatment of advanced pancreatic carcinoma [15]. In vitro data suggest activity of gemcitabine in prostate cancer cells [16].

In the above mentioned series of SAKK phase II trials, measurable response was documented in the subset of patients with measurable disease but the primary endpoint in all patients was response of PSA levels [13, 14]. Selected QL measures and the use of pain medication were assessed to describe patients’ experience of toxicity and palliation. Preliminary results of the present study were published in abstract form [17, 18]. A list of participating institutions and investigators is included at the end of the article.

Patients and methods

For study inclusion progression of a histologically or cytologically proven prostate cancer of either nodal stage D or metastatic bone stage D, had to be documented under previous endocrine therapy. WHO performance status had to be 2 or less, age less than 80 years and the life expectancy at least three months. Measurable and non-measurable disease was allowed. Bone lesions were considered to be non-measurable. The following laboratory values were required: serum level of PSA of at least three times the upper normal level, leukocytes (WBC) ≥ 3.5 × 10^9/l or granulocytes ≥ 2 × 10^9/l, hemoglobin ≥ 100 g/l and blood platelets > 100 × 10^9/l; serum creatinine < 180 μmol/l; bilirubine < 30 μmol/l, prothrombin time (PT) and partial thromboplastin time (PTT) 1.5 × the upper norm, SGPT or SGOT < 3 × the upper norm or < 5.0 × the upper norm in patients with metastatic liver disease. No previous therapy with cytostatic agents, including estramustine, was allowed. Radiotherapy had to be stopped at least three weeks prior to enrollment into the trial. Informed consent was obtained according to the regulations of local ethics committees. During the study period, therapy with LH-RH agonists had to be continued, whereas treatment with antiandrogens had to be stopped one month before study enrollment in order to distinguish between antiandrogen withdrawal effects and efficacy of the study drug.

In the present study a prolonged infusion of 1200 mg/m^2 given over 2 hours every 3 out of 4 weeks was chosen for a maximum of 10 cycles. Prolonged infusion was based on in vitro data of Eli Lilly suggesting better efficacy. Phase I trials have been performed using the prolonged infusions schedule of gemcitabine. The maximally tolerated dose (MTD) in patients with acute leukemia was 4800 mg/m^2 given on a weekly schedule in three out of four weeks at an infusion rate of 10 mg/m^2/min, whereas in solid tumors doses of the same schedule were investigated for phase II trials were between 1200 and 2249 mg/m^2. A presumably cautious dose of 1200 mg/m^2 given over two hours was chosen for the present study.

Gemcitabine (Gemzar® provided by Eli Lilly) was supplied as a lyophilized powder in sterile vials containing 200 mg or 1 g of gemcitabine as the hydrochloride salt, mannitol, and sodium acetate. Drug vials were reconstituted with normal saline added to the vial to make a solution containing 10 mg/ml or less. An appropriate amount of drug was prepared with 250 cc of normal saline and administered as an intravenous infusion over two hours. For antiepithelial treatment metoclopramide as a single drug was suggested, but the choice of the actual supportive treatment was left to the investigator.

Treatment was stopped after 10 cycles or in case of tumor progression (according to PSA levels and/or clinical criteria, which were either progression of known lesions or appearance of new metastases on X-rays or bone scans), unexpected severe toxicities, refusal by patient, or any other serious medical complication. Toxicity was assessed according to WHO criteria.

Clinical and laboratory assessment including weight, performance status (WHO), pain intensity (WHO) and serum PSA were repeated monthly before each cycle. Blood counts were done weekly. Radiological examinations consisted of a bone scan, bone X-ray if applicable, computerised tomographic scan of the abdomen, and chest X-ray at study entry and according to clinical judgement thereafter. Electrocardiography was required at study entry. For the subset of patients with measurable disease, tumor response was evaluated according to EORTC criteria.

The definition of response was primarily based on PSA levels: A complete remission (CR) was defined as normalization of PSA levels, determined at two subsequent examinations at a minimum interval of two weeks. A partial remission (PR) was defined as a decrease of PSA levels by at least 50% compared to baseline, confirmed by a second determination at a minimum interval of two weeks. For both CR and PR no increase in the size of pre-existing lesions, no appearance of new lesions and no increase of tumor associated pain score (WHO) were allowed. Progression (PD) was defined as increase of PSA levels by at least 50% compared to baseline, confirmed by a second determination at an interval between one to two weeks. Those conditions which could not be classified as CR, PR or PD were defined as no change (NC) if the duration was at least four months.

Pain treatment was not standardized, but recorded and classified by the treating physician at registration, on day 8, at monthly visits and at treatment failure.

A pain treatment score was calculated according to Moore et al. [11] for each visit by an external physician. The use of standard tablets or capsules of non-narcotic analgesics was assigned one point each; standard doses of narcotic analgesics were assigned two points (e.g., hydromorphone 2 mg, morphine 5 mg, etc.). These points were totaled for a daily score and averaged into a score assessing the week before the clinical visit.

Quality of life (QL) was assessed by the EORTC QLQ-C30 [19]. All scales and single-items were transformed according to the EORTC guidelines to range from 0–100. 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 and one for coping efforts were included. These indicators were transformed accordingly (0–100), with higher scores indicating better QL. Physican-rated pain (WHO) was also transformed to a scale from 0–100 to be comparable with patient-rated pain. All questions referred to experience during the previous week. Pain (QLQ-C30, items Q9 + Q19), fatigue and global health status/QL were prospectively defined as primary QL endpoints, 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., eight weeks), either a decrease of ≥ 2 response categories (corresponding to ≥ 33%) in the pain scale (Q9 + Q19) without an increase in analgesics, or a decrease by ≥ 50% in analgesics without an increase in pain, was required.

Changes in QL measures from baseline to subsequent timepoints were investigated by the Wilcoxon signed rank test. To test whether PSA response was associated with changes in QL, patients were grouped into two categories: CR/PR or NC versus PD. The Wilcoxon rank sum test was used to examine the difference between these two categories in each QL measure as the change from baseline over the first two cycles; thereafter, the numbers in the subgroups were too small for meaningful testing. Changes within patients and differences between groups which were present in means but not in medians (i.e., median = 0) were not considered relevant, even in case of statistical significance. Although the transformation of the QLQ-C30 scales resulted in scores ranging from 0–100, these scores 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.

All tests were two-sided. No adjustment was made for multiple testing.
Results

Fourty-three patients were enrolled from the end of October 1995 to October 1997 in member institutions of the Swiss Group for Clinical Cancer Research (SAKK) and were evaluable for analysis. Participating oncologists and institutions are acknowledged at the end of the article. Sixteen patients had measurable disease. Patient characteristics and tumor localisations at study entry are listed in Tables 1 and 2, respectively.

A total of 172 treatment cycles (median: 3 cycles/patient, range 1–10) were given. Overall, treatment was stopped prematurely in 27 patients due to progressive disease and in 13 patients due to toxicity, toxicity-associated patient refusal or complications. Thirty-two of forty-three patients had at least two cycles rendering them evaluable for PSA response. In 11 patients treatment had to be stopped before completing 2 cycles. In 5 patients treatment was completed for allplanned 10 cycles.

Doses had to be reduced in 67% of all cycles. The most common toxicity was hematological with 48% of all doses reduced due to low values of leukocytes or platelets according to predefined criteria. The worst grades of toxicities by patient are summarized in Table 3. Treatment- and disease-related reported adverse events included central neurotoxicity (later revealed as opioid intoxication), E.coli septicemia, erythema of both legs with purpura, increasing pain, hip fracture, pulmonary emboli, thrombophlebitis, congestive heart failure and subsequent treatment delay, renal failure, pulmonary infection, worsening of general state of health, a case sigmadiverticulitis and tumor-related lethal pancytopenia, both resulting in the patients’ death. The latter patient had blood values at study entry below the required minimum levels. Although thus ineligible according to study entry criteria, the patient was included in the present analysis.

Three of the forty-three study patients (RR = 7.2%) or three of thirty-two patients evaluable for PSA response (RR = 9.4%) showed a PSA response (one CR and two PR). Time to treatment failure in these three patients was 8.7, 6.6 and ≥ 9.3 months, respectively. Seven patients (16%) achieved stable disease (NC) lasting for at least four months. In some of these patients minor PSA responses were thus seen in 10 of 32 (31.6%) patients evaluable for PSA, respectively. One of the patients with NC according to PSA levels showed a clinical PR with regression of lymph node metastases.

The only observed objective remission among 16 patients with measurable tumor lesions. Another patient with NC completed the 10 cycles foreseen by the protocol and still had stable disease one month thereafter. In two patients progressive disease was noted during the tenth cycle of treatment.

Of all expected QL forms, 202 (94%) were received, 185 (95%) at baseline and 161 (93%) under treatment. QL data were evaluated up to and including cycle 5; too few patients were left thereafter due to tumor progression. Patients indicated a considerably impaired health status/QL at baseline (n = 41, median = 50), which did not significantly change under treatment. Similarly, there
was severe fatigue at the beginning of treatment ($n = 41$, median = 55.6) with no subsequent change. At day 8 of the first gemcitabine cycle, there was no substantial worsening by short-term side-effects in any of the QL measures. Emotional functioning was the only secondary endpoint with changes over time, indicating some improvement from baseline ($n = 41$, median = 66.7) to the end of cycles 2 ($n = 19$, median change = 8.3, $P = 0.07$), 3 ($n = 14$, median change = 16.7, $P = 0.1$) and 4 ($n = 9$, median change = 16.7, $P = 0.04$).

At baseline, 5 out of 41 patients with QL data stated that they experienced pain (Q9) 'not at all', 14 experienced 'a little' pain, 16 'quite a bit' and 6 'very much': more than half of the patients indicated considerable pain at the start of treatment. When asked about the interference of pain with their daily activities (Q19) 25 patients (62%) reported 'quite a bit' or 'very much'. As shown in Figure 1, palliation was documented by a significant improvement in patient-rated pain scores (Q9 + Q19) from baseline ($n = 41$, median = 50) to the end of cycles 1–3 (borderline) and 4. A similar improvement was indicated by physician-rated pain intensity from baseline ($n = 43$, median = 50) to the end of cycles 1–3.

Overall, the pain treatment scores indicated a less intensive treatment by analgesics at the end of gemcitabine cycles 1 ($n = 36$, median change = −1, $P = 0.05$), 2 ($n = 23$, median change = −2, $P = 0.006$) and 3 ($n = 16$, median change = −1.5, $P = 0.03$) as compared to the baseline ($n = 43$, median = 4.4).

Pain scores recorded by patients (Q9 + Q19) and pain treatment as combined endpoint revealed palliation in 32% of all cases. For at least 2 consecutive cycles, 14 of the 43 patients (32%) indicated either a decrease of ≥2 response categories (corresponding to ≥33%) in the pain scale from baseline without an increase in analgesics, or a decrease by ≥50% in analgesics without an increase in pain. Nine of these patients had CR/PR or NC by PSA levels, five had PD. As described in Table 4, also the patients in the latter group did likely benefit from cytotoxic therapy.

QL was compared between the patients with either CR/PR or NC and those with PD over the first two cycles. One additional patient was included as NC for this evaluation since his PSA level decreased for two cycles and the patient went off treatment during cycle 3 due to an accident considered unrelated to either the disease or treatment. The association with PSA response is summarized for measures with significant differences in Table 5: In case of CR/PR or NC, there was an improvement in global health/QL, pain, cognitive functioning and coping as compared to baseline; in case of PD, there was less pain, especially after cycle 2.

**Discussion and conclusions**

Gemcitabine, at the dose and schedule given in this study had limited objective activity in patients with advanced hormone refractory prostate cancer. Using PSA response as a surrogate marker of tumor response, only three of 43 patients (7%) enrolled in the study showed a response, with time to tumor progression ranging from 6.6 to ≥9.3 months. In seven additional patients a period of stable disease was reached with time to tumor or marker progression ranging from 6.1–11.7 months. In 1 of 16 patients with measurable tumor
The consistent improvement in both physician and patient-rated pain may at least partially be attributed to the treatment effect of gemcitabine. The changes in patient-rated scores were substantial [21]. However, given that the experimental drug was investigated in a non-randomized design, other effects, such as increased medical attention, re-evaluation and adaptation of pain medication by the study physicians or even a placebo effect cannot be excluded. Interestingly, even five patients with progressive disease in terms of PSA level indicated some palliative benefit by the cytotoxic treatment.

The latter observation raises several possible explanations, one being a higher emphasis on symptomatic pain management by the study physicians. Enrollment into the study usually led to a change of the treating physician. Alternatively, there may be an effect of gemcitabine on pain via a different mechanism than direct tumor inhibition as indicated by changes of PSA levels. Such mechanisms may include a change in the pattern of local cytokine secretion or an effect on non-tumorous cells. Only further studies, including randomized controlled trials, will more clearly delineate the beneficial effect of the study drug.

Interestingly, a discrepancy between clinical or PSA responses and pain response has been observed also by others. Dowling et al. [22] noticed in their randomized study [12] that 24% of their patients with rising PSA levels had nevertheless a palliative response. In a previous SAKK trial [13] using carboplatin in a similar patient population 26% (7 of 27) of patients had an improvement of pain or decrease of analgesic consumption with no clear-cut association with PSA responses noted.

The positive relationship between response or no change by PSA levels and some important QL domains is a further indication of palliation by gemcitabine. The improvement in cognitive functioning in patients with CR/PR or NC probably reflects the impact of reduced intake of narcotics in this group. Regarding the total sample, it has to be stressed, that there was a substantial improvement only in pain but not in the other two primary QL endpoints. Thus the beneficial impact on QL overall was limited and far from satisfactory.

In conclusion, gemcitabine given in the dose and schedule indicated above has a beneficial impact on pain in patients with hormone-refractory prostatic carcinoma in spite of only limited activity concerning PSA response. In view of considerable, especially hematological toxicity, the regimen used in the current study cannot be recommended for use in daily clinical practice.

*Appendix*

References


Received 3 September 1999; accepted 10 January 2000.

Correspondence to:
Dr R. Morant, MD
Onkologisches Ambulatorium
Klinik C für Innere Medizin
Kantonsspital
9007 St. Gallen
Switzerland