

Salvage chemotherapy for hormone-refractory prostate cancer: Association of Adriamycin and ifosfamide

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Received May 13, 2010; Accepted July 28, 2010

DOI: 10.3892/etm.2010.138

Abstract. Prostate carcinoma is the most common cancer in men. Hormone-resistance is the natural history of this metastatic disease and requires the use of docetaxel as the standard chemotherapy. At present, there is no approved second-line treatment. Here, we report a combination of treatment with Adriamycin and ifosfamide in a series of 7 relatively young patients with an average age of 57 years at the time of diagnosis. Chemotherapy was administered over 3 days with the following schedule: 20 mg/m² Adriamycin per day and 1-1.5 mg/m² ifosfamide per day, in association with Uromitexan. Treatment was repeated every 3 weeks. Three biological responses, one CT scan response, one bone scan response and two CT scan stabilizations, were obtained. Mean survival following this combination was 6.6 months, and over 26 months after first-line chemotherapy. Tolerance was good with the use of granulocyte-colony stimulating factors. Our observations clearly show that the use of this type of salvage therapy for relatively young patients in good physical condition should be further assessed in a clinical trial, particularly when different lines of chemotherapy are required.

Introduction

Prostate cancer, the most common malignancy in men and the second cause of death after lung cancer, is a public health issue in Western countries. Its incidence increases with age, with a mean age at diagnosis of 72 years.

There is much discussion regarding mass screening, with two recent international trials resulting in conflicting opinions on this subject (1,2).

For the last 50 years, standard treatment for prostate cancer at the metastatic stage has been androgenic blockage with surgical and, in particular, chemical castration using LHRH

analogues. Although more than 80% of patients respond to this treatment (sometimes for prolonged periods), the evolution of the disease, on average 24-36 months, is always towards hormone resistance. This is generally identified by recurrence of an elevation in prostate-specific antigen (PSA) levels and/or the appearance of clinical symptoms.

The addition of an antiandrogenic agent, constituting a complete androgenic blockage (CAB), sometimes enables achievement of a new response. Following this, cessation of the antiandrogenic agent (called the withdrawal effect) induces a new biological response for a period of 6-8 months in 30% of cases. Yet, prostate cancer becomes hormone refractory as the disease progresses, despite these secondary hormonal manoeuvres. In the hormone-refractory phase, mean survival is 20 months (12).

The prognosis for hormone-refractory prostate cancer (HRPC) is associated with performance status, progression of the disease and damage to internal organs or to numerous bone sites, the presence of bone pain, the Gleason score and levels of LDH, alkaline phosphatase and haemoglobin (3,4).

Prostate cancer has long been considered chemoresistant. A review of 26 trials conducted between 1988 and 1991 found a rate of response to chemotherapy of 8.7% (5). However, with a clear predominance of localisation in bone, which is not measurable, the assessment criteria for response to chemotherapy have been difficult to define.

In 1989, Fero *et al* (6) were the first to report that the change in PSA level may be used as an indicator of response to treatment in patients included in clinical trials. Several trials (7-9), and in particular a retrospective assessment of the SWOG 99-16 study (10), revealed a significant correlation between survival and a more than 50% decrease in PSA levels with treatment. This indicated the use of the PSA level as a good 'surrogate' marker in patient follow-up. Monitoring PSA levels has enabled the detection of the appearance of androgen-independent agents at a much earlier, often clinically asymptomatic, stage. Yet, it has also become more and more important to consider the effects of treatment on the quality of life as well as bone pain, in addition to the impact on lesions which are measurable using classic techniques and which are only present in 20% of patients. In order to reach a consensus regarding criteria relevant to the response to treatment, Bubley *et al* (11) proposed criteria for eligibility and response to treatment, which were used in trials concerning HRPC in 1999. These criteria have been redefined recently (12).

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Key words: prostate, hormone-refractory, chemotherapy

Eligibility criteria are based on demonstrating that the disease is progressive, and this is defined using three factors, in combination or not: i) progression of lesions, which can be measured using classic techniques; ii) scintigraphic progression (at least two new lesions on the scintigram); and iii) progression of PSA levels (the authors suggest that two successive measurements of PSA levels be taken, with a value of >5 ng/ml).

Regarding criteria for response or progression, a decrease in PSA levels is considered to be significant when it is more than 50% of the baseline with confirmation more than 4 weeks later. Progression is defined as an increase of more than 25% in the PSA level compared to the baseline, which is also confirmed by a second measurement.

For many decades, a great number of anticancer agents have been tested for the treatment of HRPC. Several periods have been identified: i) the 'pre-PSA' era, where methodology and data collected from patients, who differed from present patients, are difficult to interpret; and ii) the 'post-PSA' era, when the use of two drugs predominated: mitoxantrone, related to anthracyclines, and more recently, docetaxel.

In 2004, when two large trials were underway involving the use of docetaxel as a first-line treatment for HRPC (13,14), the Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Program in Evidence-Based Care (CCOPEBC) carried out a review of the literature from 1966 to 2004 (15) and identified approximately 80 clinical trials involving various non-hormonal treatments for HRPC. Twenty-seven trials which randomized more than 50 patients were short-listed and analyzed. Between 1979 and 2001, six trials assessed the effectiveness of estramustine and found no improvement in tumour response rate or in overall survival. Three of these six trials, however, found a significant response rate in terms of PSA, but substantial toxicity at the digestive and cardiovascular levels (16,17 and Berry W, *et al*, *Proc Am Soc Clin Oncol* 20: abs 175, 2001). In 2004, one trial assessed the effectiveness of vinorelbine in 414 patients (18) without demonstrating a difference in terms of overall survival, while the clinical benefit (measured by the change in the performance status of the analgesic scale) was significantly better in this group (30.6 vs. 19.2%, $p=0.008$). Between 1996 and 2002, three main trials assessed mitoxantrone. Based on the findings of these studies, mitoxantrone was defined as the standard first-line treatment before the docetaxel era. In addition, Kantoff *et al* (19) randomized 242 patients between an group with prednisone alone and an group with prednisone + 14 mg/m² mitoxantrone. No difference was found in overall patient survival, but a difference was noted in the level of PSA response and a longer mean time to progression (8.1 vs. 4.1 months, $p=0.018$). Berry *et al* (20) also found a difference in favour of the group administered mitoxantrone in terms of PSA response and time to progression. Finally, Tannock *et al* published the results of a randomized trial (21) comparing treatment with prednisone alone and prednisone with 12 mg/m² mitoxantrone in 161 patients. The main judgement criteria was effectiveness in reducing pain and a decrease in analgesics. An advantage was found in the group which combined prednisone and mitoxantrone, with a duration of response in terms of a decrease in pain of 42 vs. 18 weeks, $p<0.0001$, and a palliative benefit in 38% of the patients treated vs. 21% in controls ($p=0.025$).

In 2004, as the CCOPEBC carried out their literature review, two large Phase III trials, TAX 327 (13) and SWOG 99-16 (12), enabled docetaxel to be defined as the new standard first-line treatment for HRPC. In the first study, Tannock *et al* (13) randomized 1,006 patients. One group received 75 mg/m² docetaxel i.v. every 3 weeks, the second, 30 mg/m² docetaxel weekly, and the third, 12 mg/m² mitoxantrone. All patients also received 5 mg prednisone per os twice a day. A significant improvement in mean survival was found (18.9 vs. 16.5 months, $p=0.009$) in the group treated with 75 mg/m² docetaxel every 3 weeks, as well as a better response in terms of pain (35 vs. 22%, $p=0.01$). The second trial by Petrylak *et al* (12) randomized 666 patients. One group received docetaxel plus estramustine and another group, mitoxantrone and prednisone. In the docetaxel plus estramustine group, the mean survival was significantly increased (17.5 vs. 15.6 months, $p=0.02$). In both trials, the PSA response rate was also significantly better in the group treated with docetaxel.

Regarding the use of anthracyclines, a review of the literature in 2008 by Petrioli *et al* (22) found 38 Phase II and 13 Phase II-III randomized trials. The first trials assessing anthracyclines for first-line treatment in HRPC date back to the 1980s, and objective response rates were found to increase by more than 38% (23,24), with the majority of patients reporting an improvement in bone pain. In 1993, a Phase II randomized trial (25) comparing the administration of 25 mg/m² doxorubicin weekly and 30 mg/m² epirubicin weekly found a PSA response of 14.8 and 20%, respectively, as well as a decrease in pain in 33.3 and 37.7% of cases. Another study by these same authors carried out in 2002 (26) confirmed the palliative effects of weekly epirubicin with a reduction in pain symptoms in 56% of patients and an improvement in the quality of life in 68% of the 131 patients assessed. Two other studies found a decrease of more than 50% in the PSA levels in 81% of patients (27) and a decrease in bone pain in more than 65% of patients (28), respectively, demonstrating the activity of anthracyclines in prostate cancer. However, the majority of these trials assessing anthracyclines alone found mean survival rates of 5-13 months, similar to those found in untreated patients.

Between 1984 and 1998, several trials assessed anthracyclines in combination in metastatic HRPC (29-31). The majority of these trials was carried before the era of PSA level detection. The data available were limited. No study found any advantage in overall survival, and only two carried out statistical comparisons in terms of the tumour response rate. One of these trials, carried out in 1992 by Laurie *et al* (29), reported an improvement in survival with chemotherapy combining 5FU, doxorubicin and mitomycin C as compared to the same agents administered as sequential treatment (8.7 vs. 7.1 months, $p=0.025$).

Several studies also assessed the effectiveness of doxorubicin combined with cyclophosphamide. In 1984, Stephens *et al* (30) compared a combination of 40 mg/m² doxorubicin + 200 mg/m² cyclophosphamide every 3 weeks to 3,600 mg/m² hydroxyurea per os. The tumour response rate was 32% in the group with the combination vs. 4% in the group with hydroxyurea. In 1992, Saxman *et al* (31) compared doxorubicin + cyclophosphamide + methotrexate vs. cyclophosphamide alone, with a tumour response rate of 18.8% in

Table I. Characteristics of the patients treated with miniMAID protocol.

| Patient no. | Age at diagnosis (years) | Gleason score | TNM stage at diagnosis | Initial PSA levels | Initial treatment | MAID |
|-------------|--------------------------|---------------|------------------------|--------------------|----------------------|----------|
| 1 | 52 | 8 (4+4) | T3 N1 Mx | 9.1 | H, 10 months | 3rd line |
| 2 | 60 | 7 (3+4) | Tx N+ Mx | | P + H, 8 months | 3rd line |
| 3 | 54 | 8 | T3b N2 Mx | 73.0 | H, 24 months + R | 4th line |
| 4 | 61 | 7 | T4 N+ M+ | 435.0 | H, 27 months + R | 4th line |
| 5 | 62 | X | T3b N1 M+ | 1.4 | H, 13 months + R | 5th line |
| 6 | 56 | 9 | Tx N+ | 16.0 | H, 9 months | 5th line |
| 7 | 54 | 6 | T3b N0 M0 | 26.6 | P + R + H, 93 months | 7th line |

H, hormone therapy; P, prostatectomy; R, radiotherapy.

the combination treatment group vs. 6% in the other group. The majority of these combination trials found significant toxicity, with more than 20% grade 3-4 neutropenia (31).

Patients and methods

In the present study, we report our experience with the use of doxorubicin and ifosfamide in 7 patients treated in the nth line for hormone-refractory cancer between 2006 and 2008. The characteristics at diagnosis of these 7 patients are shown in Table I.

Mean age at diagnosis was 57 years. Six patients who were at a locally advanced stage at the time of diagnosis (N+, 2) had previously undergone a prostatectomy. The 'miniMAID' protocol consisted of administration over 3 days of 20 mg/m² doxorubicin per day and 1-1.5 mg/m² ifosfamide per day associated with Uromitexan, renewed every 3 weeks.

Results

Efficacy. Patient no. 1 received the miniMAID protocol in the third line after 10 months of hormone therapy, 3 cycles of Taxotere with progression in the form of carcinomatous meningitis (treated with intrathecal injections of methotrexate and radiotherapy) and 6 cycles of carboplatin. The PSA level prior to treatment was 327. The targets were mediastinal (the largest measuring 25 mm), right subclavicular, celiomesenteric, bilateral iliac and left inguinal lymph nodes. After 3 cycles, a scan showed stability of the target nodes, but with biological (PSA, 646) and scintigraphic progression (a new fixation at the level of the left tibial diaphysis associated with aggravation of the existing diffuse hyperfixations). The patient succumbed 3 months after the third cycle.

Patient no. 2 received the miniMAID protocol in the third line (with 1 mg/m² ifosfamide per day) after 8 months of hormone therapy, 9 cycles of Taxotere, 2 cycles of carboplatin and a clear aggravation in the bone scintigram. The targets were mediastinal, lateroaortic, celiomesenteric and portocaval lymph nodes, as well as three hepatic lesions, 7, 12 and 10 mm in size. Assessment after 3 cycles found biological stabilization (PSA, 38.6) and a significant response from mediastinal lymph node targets, as well as stability of hepatic and abdominal targets. Assessment after 6 cycles found a biological response

(PSA, 5.7), stability after scan and scintigraphic improvement. Secondary prophylaxis with 50 mg/day Endoxan was then started with a response maintained for 3 months, after which the patient received oral etoposide for 3 months. The patient succumbed 9 months after the last cycle.

Patient no. 3 received the miniMAID protocol in the fourth line after 24 months of hormone therapy, 9 cycles of Taxotere, 6 months treatment with Endoxan per os, 4 months of carboplatin, with an evident biological and clinical progression (appearance of brain metastases treated surgically and with radiotherapy). PSA was then at 329. The CT scan found measurable lymph node targets and diffuse bone lesions, for which he had already received radiotherapy in the spinal column (R3 and R4) and left shoulder. After the second cycle, a clinical response was observed with a decrease in the consumption of analgesics. The patient presented subcutaneous inflammation around the implantable infusion pump with neutropenia, justifying hospitalization and removal of the pump. Assessment after 4 cycles found biological stability (PSA, 379), but progression in target tumours. Despite starting treatment with Xeloda, the patient succumbed 2 months after the fourth and last miniMAID cycle.

Patient no. 4 received the miniMAID protocol in the fourth line after 27 months of hormone therapy, more than 1 year of oral chemotherapy with Navelbine, 9 cycles of Taxotere, 3 cycles of carboplatin; in total, approximately 6 years of treatment after the initial diagnosis of a disease, which was metastatic from the outset in bone and lymph nodes. The PSA level was at that time 4,421. The CT scan found mediastinal and retroperitoneal target nodes. Scintigraphy showed that numerous hyperfixing sites had appeared with carboplatin. After 3 cycles there was a biological response (PSA, 2,800) and a clinical benefit as far as pain was concerned. After 6 cycles, the outcome was a biological response (PSA, 2,571) and stabilization of target tumours and bone scintigram. The patient succumbed after presenting carcinomatous meningitis 2 months after the last cycle.

Patient no. 5 received the miniMAID protocol in the fifth line after 6 cycles of Taxotere, 2 months of Endoxan, 2 cycles of carboplatin and 3 cycles of Novantrone. The PSA level was 330 at the beginning of treatment. There were mediastinal and retroperitoneal target nodes. After 3 cycles, the PSA level was at 427, but bone scintigraphy showed tumour stability. It was

Table II. Assessments at the third or fourth cycle.

| Patient no. | Pre MAID PSA levels | Location of metastases | PSA levels | CT scan | Scintigraphy |
|-------------|---------------------|--|--------------------|-------------|--------------|
| 1 | 327 | Diffuse - bone Diffuse - lymph nodes | Progression (646) | Stability | Progression |
| 2 | 39 | Diffuse - bone Diffuse - lymph nodes Three hepatic locations | Stability (38.6) | Response | |
| 3 | 329 | Diffuse - bone Diffuse - lymph nodes | Stability (379) | Progression | |
| 4 | 4,421 | Diffuse - bone Diffuse - lymph nodes | Response (2,800) | | |
| 5 | 330 | Diffuse - bone Diffuse - lymph nodes | Progression (427) | | Stability |
| 6 | 24 | Bone and lymph nodes Peritoneal carcinomatosis | Response (7.5) | Response | |
| 7 | 11,874 | Bone and lymph nodes Diffuse hepatic infiltration | Stability (12,593) | Stability | |

Table III. Assessment at the sixth cycle.

| Patient no. | PSA levels | CT scan | Scintigraphy | Conclusion after 6 cycles |
|-------------|------------------|-------------|--------------|---|
| 1 | | | | |
| 2 | Response (5.7) | Stability | Response | Biological and scintigraphic response Stability CAT scan |
| 3 | | | | |
| 4 | Response (2,571) | Stability | Stability | Biological response Stability scintigraphy and CAT scan |
| 5 | Progression | Progression | Progression | |
| 6 | Response (4.1) | Response | | Biological and CAT scan response |
| 7 | | | | |

decided to continue treatment for up to 6 cycles. At the end of the treatment, CT scan assessment showed a progression of bone and lymph node targets. The PSA level was 399. The patient succumbed 6 months after the last cycle.

Patient no. 6 also received the miniMAID protocol in the fifth-line treatment after 5 cycles of Taxotere, 6 cycles of carboplatin and etoposide, 8 months of Celltop per os at 50 mg/day and 10 months of Endoxan per os at 50 mg/day. The PSA level was 24. The CT scan found target nodes as well as peritoneal carcinomatosis, with a 66-mm right pararenal mass and a 45-mm retroperitoneal mass. After 3 cycles there was a biological (PSA, 7.3) and a tumoral response, with a decrease in target nodes. It should be noted that this patient had an episode of febrile aplasia in the second cycle with grade 4 neutropenia (leukocytes at 100/mm³), justifying a short hospitalization for the administration of antibiotic treatment and monitoring. After 6 cycles, a tumoral response was maintained with a new overall decrease in node formation of 13%. The PSA level was 4.1 at the end of the treatment. After 3 months with no treatment, there was tumour stability and a PSA of 6. Five months after the last cycle, faced with biological progression, a sixth-line treat-

ment with Xeloda was instituted. The patient succumbed 4 months later.

The last patient, no. 7, received the miniMAID protocol in the seventh line, more than 13 years after the initial diagnosis of locally advanced cancer and after 93 months of hormone therapy, 3 cycles of Endoxan, 8 cycles of Taxotere, then Distilbene for nearly 15 months, Navelbine, 3 cycles of carboplatin, Celltop for 3 months, without any response, and inclusion in a Phase I trial to assess Enzastaurin. Assessment at 2 months showed an increase in hepatic infiltrate and progression in retroperitoneal target nodes of 27%, justifying exit from the trial. He was then offered the miniMAID protocol. Although early assessment after 2 cycles showed biological (PSA, 12,593) and CT scan stability, the patient presented a cave syndrome near the end of the third cycle, justifying cessation of chemotherapy. He was then put back on Distilbene with an interesting clinical and biological response (PSA 9,336 at 2 months). He is currently on Xeloda and has been since March 2009.

Collectively, this treatment enabled us to obtain three biological responses in the 7 patients treated, as well as one CT scan response, one bone scan response and two CT scan

Table IV. History of the disease.

| Patient no. | Start of hormone therapy | Start of chemotherapy | Start miniMAID | Death | Overall survival to hormone refractory stage (months) |
|-------------|--------------------------|-----------------------|----------------|---------------|---|
| 1 | Beginning 2004 | July 2005 | March 2006 | August 2006 | 13 |
| 2 | July 2004 | October 2005 | September 2006 | October 2007 | 24 |
| 3 | September 2004 | September 2006 | June 2008 | October 2008 | 25 |
| 4 | August 2002 | September 2005 | May 2008 | November 2008 | 38 |
| 5 | October 2005 | May 2007 | April 2008 | January 2009 | 20 |
| 6 | September 2004 | August 2005 | April 2008 | January 2009 | 41 |
| 7 | Mid-1995 | Beginning 2007 | September 2008 | Still alive | >24 |

stabilizations with regard to imaging examinations (Tables I and III). Mean duration of survival from the beginning of treatment with chemotherapy was calculated to be more than 26 months, with a variance of 13 months at more than 41 months (Table IV). Mean duration of survival from the start of the miniMAID protocol was calculated to be 6.6 months. There was a good correlation between the biological response measured by the PSA level and tumour response assessed clinically and by imaging techniques.

Toxicity. All of the patients in this cohort had cardiac assessment with ultrasound and measurement of the left ventricle ejection fraction before treatment began. On retrospective analysis of the data, no cardiac toxicity was reported. All patients had haematopoietic leukocyte growth factor support during the inter-cycle periods. Two episodes of febrile aplasia justifying hospitalization were reported in 2 patients; one rapidly resolved without complication towards the end of the second cycle; the other, also related to cellulitis, was resolved towards the end of the second cycle. The majority of patients had support in the form of packed red blood cell transfusion. It was difficult to balance medullary deficiency through tumour invasion with direct haematological toxicity from the drugs used.

Discussion

Treatment of HRPC has seen great advances over the last 20 years, in particular improvements in assessing the response to treatment by measuring PSA levels.

Docetaxel is considered to be the chemotherapy of choice in first-line treatment, as data concerning other possible treatments are sparse and, though sometimes encouraging, often outdated and difficult to apply, and in any case not standardized from the second line of treatment.

Anthracyclines are among the most important anti-cancer agents with a wide spectrum of antitumoral activity. Anthracyclines may also induce apoptosis in prostate cancer cells expressing the bcl-2 oncogene. The activity of anthracyclines in prostate cancer has already been demonstrated (22-28,30,31).

Cyclophosphamide is a drug which has also shown activity in prostate cancer, in particular, metronomic per os and in cycles. Ifosfamide, an analogue of cyclophosphamide,

is an alkylating intercalator agent which interacts directly with DNA, resulting in cell death by apoptosis. It appears to be more effective than cyclophosphamide, in particular in the treatment of sarcoma, where it has been most extensively studied (32).

In addition, a synergistic effect in combining this alkylating agent with anthracyclines has been noted (33). To our knowledge, there is little data concerning the use of this drug in the treatment of HRPC. Some phase II trials, consisting of less than 30 patients, have shown mixed results (34,35).

More recently, studies have assessed the combination of anthracyclines and taxanes, and have demonstrated promising results. For example, a weekly combination of 30 mg/m² epirubicin plus 30 mg/m² docetaxel in 38 patients achieved a decrease in PSA levels in 68.4% of cases and a decrease in pain in 72.7% of cases (36).

Although the present study was a retrospective analysis of a small number of patients, it emphasizes several important points in the history of prostate cancer. Prostate cancer has long been considered to not be sensitive to chemotherapy. Due to this fact, response criteria must be defined that are different from those of other tumour types. The responses found in this cohort of patients in nth-line treatment demonstrate the chemosensitivity of this cancer. Although a consensus has been made with regard to first-line treatment with docetaxel based on its benefit in overall survival in two large well-conducted studies, from the second line onwards no notable result has been found. However, other available drugs, when administered sequentially in clinical practice to patients in overall good physical condition, show an incidental activity on survival. Our cohort of patients, directly N+, having had up to 7 lines of chemotherapy and with a mean survival of more than 26 months from the institution of chemotherapy, is one example. Of course, the patients were relatively young, with a general state that permitted this incisive treatment.

The majority of trials using anthracyclines in association with cyclophosphamide were carried out before the use of surrogate response markers, such as PSA levels, and with questionable methodologies. The rate of response found in our cohort treated in the nth line suggests that anthracyclines used in combination with ifosfamide may have a much greater activity than that demonstrated previously. This promising result requires further investigation and verification with Phase II trials.

In conclusion, metastatic HRPC is characterized in more than 80% of cases by bone damage causing pain, the objective assessment of which is difficult. Over the last few years, appropriate assessment criteria have emerged.

Docetaxel is the standard chemotherapy in first-line treatment, but there is a wide panel of classic drugs available which, when used in combination, are potentially effective. At present, after first-line treatment, two paths are evident: i) to develop new protocols for combined chemotherapy, or ii) to turn to new types of treatment, such as anti-angiogenics, or treatments more specific to bone damage, such as inhibitors of the receptor of endothelin A. These multiple options emphasize the growing complexity of the management of prostate cancer and the need to include patients in clinical trials. Assessment of anthracyclines in combination with ifosfamide in a prospective second-line treatment trial after failure of docetaxel is warranted.

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