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Effective low-toxicity oral combination metronomic chemotherapy for the management of castration resistant prostate cancer

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Background:

Prostate cancer was previously believed to be a chemoresistant disease. In recent years taxane based chemotherapy has been shown to prolong survival in patients with castration resistant prostate cancer (CRPC). However, it remains to be shown which type of chemotherapy gives the best effect with the least amount of side effects.

Materials and methods:

17 patients with chemo-naïve CRPC were enrolled/included in a pilot study evaluating an orally administered (metronomic?) chemohormonal treatment regimen including a weekly sequential combination called KEES; consisting of Ketoconazole in combination with Cyclophosphamide or Etoposide in combination with Estramustine given on alternate weeks. Prednisone was administered throughout the treatment period. Prostate-specific antigen (PSA) response, acute and chronic toxicities were evaluated.

Results:

11 (65%) patients achieved a PSA reduction with a median of 87% (range 26%-99%). 9(53%) patients responded with a decrease in PSA > 50%. Thrombocytopenia (4/17 or 24%) and anaemia (3/17 or 18%) were the most common side effects noted. One study fatality was reported, however, it is unclear if this was treatment related.

Conclusions:

KEES may be a promising option for patients with CRPC, resulting in a clear reduction of PSA with limited toxicity. Further clinical evaluation of this metronomic chemohormonal combination is warranted

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Introduction

Prostate cancer (PC) is a common and extremely variable disease ¹. A big challenge is the large group of patients, around 40%, which after radical treatment (surgery or radiation therapy) relapse. Standard therapy for these patients is castration leading to a temporary decrease in tumor growth. Unfortunately, this effect is transient and sooner or later (median 18-24 months) tumor growth will resume to a hormone independent phase, so called castration resistant prostate cancer (CRPC), eventually resulting in death due to wide spread disease ¹. Until recently, few treatment options have been available for these patients.

For many years PC was believed to be a chemoresistant disease ^{2,3}. Clinical trials with mitoxantrone in the late 90 ´s showed only palliative effects in patients with CRPC ⁴. In 2004 two large randomised phase III trials (the Southwest Oncology Group's (SWOG) 99-16 and Tax 327 studies) showed that docetaxel based therapy not only improves quality of life and decreases pain but also prolongs survival in patients with CRPC ^{5,6}. Thus, for the first time, chemotherapy may be considered a treatment option for patients with CRPC where taxane based therapy is considered to be the gold standard. The drawbacks of treatment with docetaxel are, however, that the effect on survival is rather small (2-3 months) and the duration of the effect is a short 6-month period. It is an expensive treatment and also causes several major side effects such as neutropenia, neuropathy and fatigue ⁷.

Patients with CRPC make out a large heterogenous group of patients ranging from asymptomatic patients where the only sign of progression is a rising PSA to patients with symptomatic metastases ^{7,8}. Furthermore, these patients are

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often old with a high degree of comorbidity. The timing and best strategy for treating different groups of CRPC patients is not clear today but there is an obvious need for clinical trials testing different chemotherapy regimens in different stages of the disease so that the optimum therapy with the most convenient routes of administration and least amount of side effects can be defined ^{3,7}.

In recent years significant advances have been made in our understanding of tumor biology in CRPC where both tumor cells as well as the surrounding stroma seem to play a pivotal role in tumor progression ⁸. Theoretically this means that the use of a combination therapy where both tumor cells and stromal cells are targeted could give a synergistic antitumor effect. There are plenty both preclinical and clinical data supporting this concept⁸. Therefore, in this study we wanted to investigate whether a combination of secondary hormonal manipulation and chemotherapy, given in a metronomic way, could have an effect in patients with CRPC.

Metronomic chemotherapy is a regimen where low doses of chemotherapy are given on a frequent or continuous schedule with no extended interruptions ⁹ ^{10,11}. Preclinical studies have shown that even though the total dose of chemotherapy is lower, the tumor inhibiting properties are just as good and in some cases even better than conventionally administered chemotherapy given as maximum tolerated dose (MTD) ^{9,10}. The main course of action for metronomic chemotherapy is thought to be by attacking tumor stroma through its antiangiogenic properties thereby interrupting oxygen and nutrient supply in tumors ^{9,10}. In patients with lung, breast- and ovarian cancer who stopped

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responding to MTD based therapy, therapeutic effects are seen when chemotherapy is given daily or weekly ¹²⁻¹⁴. Furthermore, maintenance therapy in children tumors such as leukemia is very similar to metronomic chemotherapy and has been used for years ¹³.

Several phase II trials with combination chemotherapy administered in a metronomic way in patients with CRPC have shown a therapeutic effect ¹⁵⁻¹⁸. One of the most promising regimens consists of ketoconazole in combination with doxorubicin alternating with vinblastine in combination with estramustine (KA/VE) ^{15,17}. In a phase II trial with 45 patients a 8-week treatment cycle produced the best response rates observed to date in this patient population: PSA reductions of > 50% in 31 patients (69%) and > 80% in 26 (58%), and a median overall survival of 18.1 months i.e. PSA responses, palliative and survival effects that compares favorably and sometimes even better than early docetaxel studies ^{15,17}. The drawback, however, was toxicity and more tolerable regimens were a high priority before going into phase III trials.

Based on these findings we developed a metronomically given peroral chemohormonal treatment schedule for patients with CRPC consisting of ketoconazole in combination with cyclophosphamide or etoposide in combination with estramustine given on alternate weeks (KEES). Prednisone was administered the entire time to counteract potential adrenal insufficiency secondary to ketoconazole. All these drugs have previously been used in prostate cancer and much attention was given to possible positive and negative interactions and toxicity when choosing dose levels.

The aim of this pilot study was to study the effect (reduction in serum PSA)

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and toxicity of the KEES protocol in 17 patients with CRPC.

Patients and methods

Patients

Between 2003-2005 seventeen patients with HRPc were included in this study at the Oncology Department, Sahlgrenska Hospital, Gothenburg and the Department of Urology, Uddevalla Hospital, Uddevalla, Sweden. No randomisation was performed. Included patients were those who personally asked for further treatment once they developed CRPC. Treatment was designed to be administered in an out patient setting. The median age was 60 years (range 40-75 years). All patients had histopathologically verified PC and had previously been treated with medical or surgical castration for a median time of 45 months (range 6 -108 months). The medical castration included androgen deprivation, oestrogen, anti-androgen monotherapy or combined androgen blockade (CAB). All patients had previously been treated with CAB for at least one period and all but three patients had experienced the effect of a therapeutic anti-androgen withdrawal. Six patients had received previous first line treatment of CRPC. All patients were screened with bone scintigraphy. Patient's clinical characteristics are presented in detail (Table I).

Chemotherapy planning

Each course of per oral chemotherapy lasted for 6 consecutive weeks, with 2 week rest between each course. Five agents were included in the KEES schedule and administered as follows: Cyclophosphamide, Sendoxan®, (50 mg twice daily) in combination with ketaconazole (200mg three times daily) were administered for seven consecutive days during weeks 1, 3 and 5. During

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weeks 2, 4 and 6 patients received seven consecutive days of etoposide (50 mg twice daily) in combination with estramustine (140 mg twice daily). One patient received idarubicin (5 mg daily 4 days a week) instead of

cyclophosphamide because of hypersensitivity. A 2 weeks rest followed each 6 week course. Prednisone (10 mg x daily) was given throughout the entire treatment period to counteract potential ketokonazole induced adrenal complications. At the start of treatment each patient was provided with a KEES schedule to aid in the correct administration of the various drugs.

Treatment planning

The baseline visit was conducted at the outpatient clinic at Sahlgrenska University Hospital and included a physical examination and blood tests: Serum PSA (Prostate Specific Antigen), Hb (Haemoglobin), WBC (white blood cell count), platelets, AST (Aspartate transaminase), ALT (Alanine transaminase), bilirubin, and creatinine. Blood tests were repeated monthly and at the start of each new course. Monthly contact with the doctor was maintained via telephone or if needed a clinical appointment. A clinical staff nurse could easily be reached and available to the patients. Prior to the start of each new chemotherapy course, a physical examination was performed.

PSA levels were used to follow the effect of chemotherapy and recorded every 8 weeks? Patients with bone metastases that demonstrated a serum-PSA reduction by at least 50% after 2-3 courses were evaluated with the intention to administer Strontium (Sr-89) if no contraindications were found. For

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patients with PSA reduction of less than 50%, a third course was administered. Patients with no bone metastases received a third KEES course, if there were no contraindications and good tolerability. No patient received more than three courses of chemotherapy. PSA response was determined by using the baseline value and the nadir value after 2-3 courses (i.e. 4-6 months) of chemotherapy.

The choice of the consolidating regime depended on the patient's symptoms and tumour burden. Those with soft tissue metastases received cyclophosphamide 50 mg/daily while those with skeletal metastases and bone pain received zoledronic acid, 4mg, monthly. In both groups treatment continued for 6 months.

Statistics

The study is a retrospective analysis and descriptive statistics were used to analyse data.

Results

PSA-response

Of the seventeen patients with HRPC treated with the KEES regime, eleven patients (64.7%) demonstrated a reduction in their serum PSA levels with a median of 87% (range 26%-99%, 95% CI 59.9-93.3). Of these 11 patients, more than a 80% reduction in PSA levels was found in seven patients (41%), three patients (18 %) had 56 – 79% reduction and one patient had a minor reduction of 26%. Nine patients (53%) responded with a decrease in PSA > 50%.

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All patients except one (11) received 2 or 3 courses of KEES over a period of 4-6 months. Although this patient demonstrated a 57% reduction in PSA one month after therapy, his general condition deteriorated due to diarrhea and he died one month after the initiation of KEES therapy. No autopsy was performed and the cause of death is unknown. Six patients (3,4,9,10,13) did not respond to treatment, since no PSA reduction was observed. For details of each individual patient's PSA level throughout the study see figure 1.

Treatment was discontinued in four patients. Three patients (3,4,13) were, in retrospect, in very poor condition at baseline and did not tolerate the chemotherapy. One patient (9) showed no response and chemotherapy was discontinued because he forgot his androgen deprivation. Eight patients (1,2,5,6,8,14,15, and 16) were eligible for Sr-89, five patients after two courses and three patients after three courses. One of these patients (2) could not be treated with Sr-89 due to thrombocytopenia. Results are presented in Table II.

Side effects and morbidity

Thrombocytopenia was the most common side effect. Four patients (2,4,13,16) or 24% demonstrated thrombocytopenia. One patient (2) needed repeated transfusions over a period of two months. Two additional patients developed delayed thrombocytopenia (4,16). Anemia was the second most frequent observed side effect. Three patients (2,4,17) or 18% developed anemia that required erythrocyte transfusions. One patient developed acute cholestasis and elevated serum creatinine after his second KEES course with a peak of 214 μ mol/L and 208 μ mol/L respectively (reference value 60-20 μ mol/L). The signs and symptoms as well as blood tests returned to normal in three weeks.

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This same patient was retreated after one year with no observed side effects, and a good secondary response was achieved. All laboratory tests prior to and after chemotherapy are presented in Table III.

Two patients (14,17) experienced vascular complications in the form of thromboembolic events. One patient (14) was initially on anti-coagulant treatment, in spite of this fact, he developed a pulmonary embolus. One patient (17) developed a deep vein thrombosis. Other observed side effects were mild gastrointestinal symptoms (29%), oedema (12%), diarrhea (6%), skin rash (6%) and elevation of liver enzymes (6%). Alopecia showed a great degree of variability from mild to severe, only one patient experienced complete alopecia. All side effects/morbidities are presented in Table IV.

One case of mortality was reported. This patients general condition deteriorated due to diarrhea and he died one month after initiation of KEES therapy (11) died one month after the start of the first course of KEES. Unfortunately no autopsy was performed and the cause of death remains unknown.

Discussion

Treating patients with castration resistant prostate cancer with a sequential metronomic chemohormonal therapy like KEES seems to be beneficial with PSA responses that compares favorably with prior reports and with less toxicity than previously described for composite chemotherapy regimens.

Even though the use of docetaxel in PC has shown a life prolonging effect it still remains only a modest alteration in the natural history of androgen

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independent prostate cancer ¹⁹. The timing and best strategy to treat the heterogeneous population of patients with CRPC, who are often older and with a great degree of comorbidity, remain largely undefined although several clinical trials are underway. Our goal must be to define the optimum therapy with the most convenient route of administration and the least amount of side effects ⁷.

The KEES protocol was designed in an era when docetaxel was not available and our aim was to create an entirely out patient based schedule with limited toxicity and per oral administration as an alternative to in-house patient use. The KEES regimen described in this report was based upon an MD Andersson ¹⁵⁻¹⁷ protocol but converted to a fully per-oral regime, therefore doxorubicin and vinblastine were replaced with cyclophosphamide and etoposide which also have an effect in prostate cancer ^{18,20,21-24}. By combining secondary hormonal manipulation (ketokonazol, estramustine) with chemotherapy (etoposide, sendoxan, and estramustin) given in a metronomic way we hoped to see a synergistic tumor antitumor effect as previously described in experimental studies ²².

The PSA responses observed in this group of patients who were treated with 2-3 courses of KEES (4-6 month therapy) where 53% of patients responded with a > 50 % decline in PSA equals the PSA response rates seen in docetaxel studies (TAX 327 and SWOG-9916)^{5,6}. However, whether this PSA reduction also corresponds to a prolonged progression free and overall survival and increased quality of life remains to be shown and is underway. Even though data is not presented in this paper several patients receiving consolidating

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therapy had lasting PSA responses (see figure 4).

The toxicity observed in this study was less than previously described for composite chemohormonal or docetaxel containing regimens. A major concern was the risk of thromboembolic complications in estramustine containing protocols which in some trials has been as high as 30%²⁵. We used a smaller dose of estramustine (140 mg twice daily) which is less than doses used in previous studies and may therefore explain why we observed less thromboembolic events (18%). A major complication in docetaxel studies has been neutropenia which was not seen at all in this trial. Thrombocytopenia was the most frequently observed side effect observed in four patients where two required transfusions but no incidences of bleeding was observed. However, eventually thrombocyte levels returned to normal levels for all four patients. Ketokonazol treatment is associated with an increased risk of liver toxicity but in our study only one patient had elevated liver enzymes which is less than previously described. To minimise the risk of liver toxicity we used low dose ketokonazole (200 mg td) which recently was shown to give equal responses as high dose ketokonazol^{26,27}. Taken together, with the exception of an increased risk of thrombocytopenia, the KEES protocol was well tolerated.

It is not possible to analyze the contribution of various components to the responses observed in this small trial but it is likely that some drugs contribute more than others. As mentioned earlier all drugs have previously been tested as single drugs or in combination for patients with CRPC. One could argue that some of the treatment effect could be contributed to prednisone which is probably true. However, single drug studies with prednisone in androgen independent PC have shown PSA response rates of 16-24% which is less than

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in our study ²⁸.

In an insightful editorial by Millikan and Logothetis this year in Journal of Clinical Oncology they conclude that although the general perception that castrate-resistant prostate cancer is inherently chemotherapy-resistant has been largely overcome, it remains true that the prolongation of survival in patients with advanced prostate cancer is modest and effective treatment combinations have yet to be developed ¹⁹. In this small preliminary report we have shown that sequentially given chemohormonal metronomic therapy seems to be less toxic than conventional scheduling but with equal effect on PSA levels. By yielding a lower accumulated dose it makes a more prolonged treatment possible which is important considering the palliative situation for patients with CRPC. A low toxicity treatment with the prospect of being used for an extended period of time with the advantage of being easy to administer and to a low cost, is in our mind the most favorable at present time

Conclusion

This small preliminary pilot study show that sequentially given metronomic chemohormonal therapy is feasible for patients with castration resistant prostate cancer.

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Legends to Tables

Table I

Clinical characteristics of the 17 patients

TUR-P = transurethral resection prostate, NC= not confirmed, CAB= combined androgen blockade, AA = anti-androgen

Table II

Treatment planning and the results measured by PSA changes

Normal serum PSA = < 3.0 ug/L

Table III

Laboratory tests before and after treatment with KEES

Table IV

Side effects/morbidity observed among patients treated with KEES

Legend to Figure 1

Prostate specific antigen (PSA) levels of all 17 patients. Numbers indicate patient number as described in Table I. Patients number 3, 4, 9, 10, 13 and 16 did not respond to therapy with reduction of PSA levels (grey lines). Patient number 4 received treatment for only 4 days. Asterisks (*) denotes patient treated with additional Strontium (Sr)-89.

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Figure 1.

