SCANDINAVIAN JOURNAL OF UROLOGY
2020, VOL. 54, NO. 2, 110–114
https://doi.org/10.1080/21681805.2020.1730435

ARTICLE

Feasibility and efficacy of sequential systemic therapy for metastatic castration-resistant prostate cancer in a rural health care setting

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ABSTRACT

Aim: The aim of this study was to evaluate the feasibility and efficacy, in terms of overall survival, of sequential systemic therapy in patients with metastatic castration-resistant prostate cancer (MCRPC) who lived in Nordland County, Norway, a large region with a challenging geography, yet only one department of oncology located in the main city, Bodø.

Patients and methods: Overall 77 patients who had received at least 2 lines of treatment were included in this retrospective study.

Results: Management included docetaxel in 69 patients (90%), often prescribed in first line. Only 12 patients (16%) started their treatment with a sequence of two endocrine drugs (enzalutamide or abiraterone acetate). Thirty-two patients (42%) were not eligible for treatment beyond second line, while 31 (40%) received 3 lines, and 14 (18%) more than 3 lines (for example cabazitaxel or Ra-223). Distance to the department of oncology did not predict for treatment with more than 2 lines. Only two factors were statistically significant: age <75 years and not initiating treatment with two lines of endocrine drugs. Survival increased with increasing number of lines of treatment. None of the five individual drugs available to these patients was significantly associated with survival.

Conclusions: There was no indication toward under-treatment with systemic therapy among patients from the distant regions. Sequential treatment was feasible and survival increased with each additional line.

ARTICLE HISTORY
Received 12 December 2019
Accepted 12 February 2020

KEYWORDS
Prostate cancer; distant metastases; chemotherapy; systemic therapy; survival; pattern of care

Introduction

Several options for systemic therapy of metastatic castration-resistant prostate cancer (MCRPC) are currently available, e.g. chemotherapy (docetaxel and cabazitaxel), endocrine-based therapy (enzalutamide and abiraterone acetate) and the radionucleotide Ra-223 [1–3]. Commonly, patients in adequate performance status and without contraindications to one or several of these approved drugs receive sequential treatment [4–7]. There is no universally agreed sequence of choice. Rather, individual decisions are made, taking into account patient preference, toxicity and disease characteristics, such as the presence of visceral metastases or the prostate-specific antigen (PSA) doubling time, to name a few. Reasons to terminate treatment and switch to a new line include intolerable side effects and disease progression. While oral medications (enzalutamide and abiraterone acetate) can be taken at home, the other drugs require travel to a hospital for intravenous injection, typically at a chemotherapy unit. In rural North Norway, travel distances to these units may exceed 200 km, and weather conditions during the winter months may result in difficulties, e.g. closed roads and airports [8,9]. Therefore, we were interested in an audit of systemic therapy sequencing, with focus on feasibility and efficacy of MCRPC treatment. Specific questions included: how many patients receive 3 or more lines of treatment, can we identify factors that predict for non-receipt, are any of the approved drugs essential for overall efficacy, and is there any preferable sequence of drugs in the first 2 lines?

The setting of care was the publicly-funded Norwegian health care system, which aims to avoid disparities and financial barriers to oncology care, e.g. by providing travel and accommodation [8–10]. Norway has been known for a policy aiming to minimize poverty and offer public health insurance to all inhabitants. The main hospital in our region and the only one with a department of oncology is located in Bodø. Systemic treatment is also administered at five smaller local hospitals, which consult with an oncologist *via* weekly virtual, web-based meetings.

Material and methods

This retrospective study included 77 consecutive men (all Caucasian) with MCRPC who received oncology care at the Nordland hospital Bodø (academic teaching hospital in rural North Norway). Some patients presented with metastases at diagnosis, others later during the disease trajectory. In all cases, systemic treatment for MCRPC was started between 2007 and 2018, and at least 2 lines were administered. Twenty-six patients (34%) were treated before enzalutamide

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Table 1. Patient characteristics, $n = 77$.

Parameter	n	%
Gleason score 8–10	42	55
Gleason score <8	35	45
Bone metastases only	49	64
Bone + distant nodal metastases	13	17
Distant nodal metastases only	11	14
Visceral metastases	4	5
First line docetaxel	53	68
Other first line drug	24	31
Any docetaxel	69	90
Any cabazitaxel	10	13
Any Ra-223	19	25
Post chemotherapy enzalutamide	32	42
Any bone targeting agent*	49	64

*Zoledronic acid, denosumab, etc.

and abiraterone acetate were generally available in Norway, i.e. before 2011. Drug therapy was given according to the National guidelines, which, however, leave room for individual sequencing. It did not include early docetaxel during the hormone-sensitive stage in this study. Enzalutamide and abiraterone acetate were never instituted for hormone-sensitive disease or non-metastatic CRPC. Cabazitaxel was instituted only after previous docetaxel therapy. Drug doses and intervals were chosen by the treating clinical oncologist and adjusted according to toxicity. For example, docetaxel could be administered every 3 weeks, every 2 weeks or once weekly. The regional electronic patient record (EPR) system, named DIPS®, was used to collect all follow-up, treatment and baseline data. Actuarial survival from the first day of systemic treatment for MCRPC was calculated with the Kaplan–Meier method and compared between subgroups with differing baseline characteristics with the log-rank test. Four patients were censored at the time of last follow-up (42–72 months, median 51 months). Associations between different variables of interest were assessed with the chi-square or Fisher's exact probability test (two-tailed). A multivariate forward conditional Cox analysis of prognostic factors for survival was performed. All parameters with statistically significant p value in univariate log-rank test were included. A p value $\leq .05$ was considered statistically significant.

Results

Patient characteristics

Median age was 69 years, range 56–88 years. In 52 patients (68%), metastases developed after an initial period of non-metastatic disease (median 63 months, range 5–220 months; 18 of these patients had non-metastatic CRPC before they progressed to MCRPC after 2–25 months, median 4 months), while 25 (32%) had distant metastases already when they were diagnosed with prostate cancer. Further patient characteristics are shown in Table 1.

Treatment details

Systemic treatment for MCRPC included docetaxel in 69 patients (90%). Typically, this drug was prescribed in first line ($n = 53$, 69%). Only 12 patients (16%) started their treatment with a sequence of two endocrine drugs (Table 2). Thirty-two patients (42%) were not eligible for treatment beyond second line, while 31 (40%) received 3 lines, and 14 (18%) more than 3 lines. We analyzed factors predicting for treatment with more than 2 lines in 73 patients (3 were excluded because only 2 lines were available when they were treated, and 1 because he was still receiving second-line treatment and was a candidate for further therapy at the time of future progression). Distance to the department of oncology in Bodø did not predict for this endpoint, regardless of cut-off in kilometers. Only two factors were statistically significant: age <75 years (72% received at least 3 lines *versus* 25% in older patients, $p = .001$) and not initiating treatment with 2 lines of endocrine drugs (67% received at least 3 lines *versus* 33% in those who started with enzalutamide/abiraterone acetate or the reverse sequence, $p = .048$).

Table 2. Pattern of care: initial 2 lines of treatment.

Drugs	n	%	Median survival
Docetaxel followed by abiraterone acetate	34	44	27.0 months
Docetaxel followed by enzalutamide	10	13	29.0 months
Docetaxel followed by cabazitaxel	5	6	14.2 months
Sequence of 2 endocrine drugs	12	16	24.0 months
One endocrine drug followed by docetaxel	8	10	10.8 months
Other sequences	8	10	Insufficient numbers

Overall survival

Median survival was 22.4 months (95% confidence interval 16.1–28.7 months). Age and synchronous presentation with metastases were not significantly associated with survival. The same holds true for pattern of metastases, even if the presence of visceral metastases resulted in shorter survival (13.7 months, bone only 22.4 months, nodal only 28.2 months, all differences $p > .1$). Treatment before 2011 (no enzalutamide and abiraterone acetate available) resulted in median survival of 21.0 months, compared to 27.6 months in the time period 2011–2018 ($p = .29$). However, interval ≥63 months was associated with longer survival (median 31 *versus* 20 months (if shorter or synchronous), $p = .002$. The number of treatment lines was also associated with survival (2 lines: 17.3 months, 3 lines: 22.0 months, more than 3 lines: 42.5 months), $p < .05$ for all pairwise comparisons (Figure 1).

Cox regression analysis

Time interval <63 months was confirmed as prognostic factor for shorter survival (hazard ratio 2.1, $p = .006$). Administration of more than 2 lines of treatment was associated with longer survival (hazard ratio 0.55, $p = .001$). None of the five individual drugs was significantly associated with survival.

Discussion

This retrospective audit of rural clinical practice was performed with four specific questions in mind: how many patients receive at least 3 lines of treatment, can we identify factors that predict for non-receipt, are any of the approved

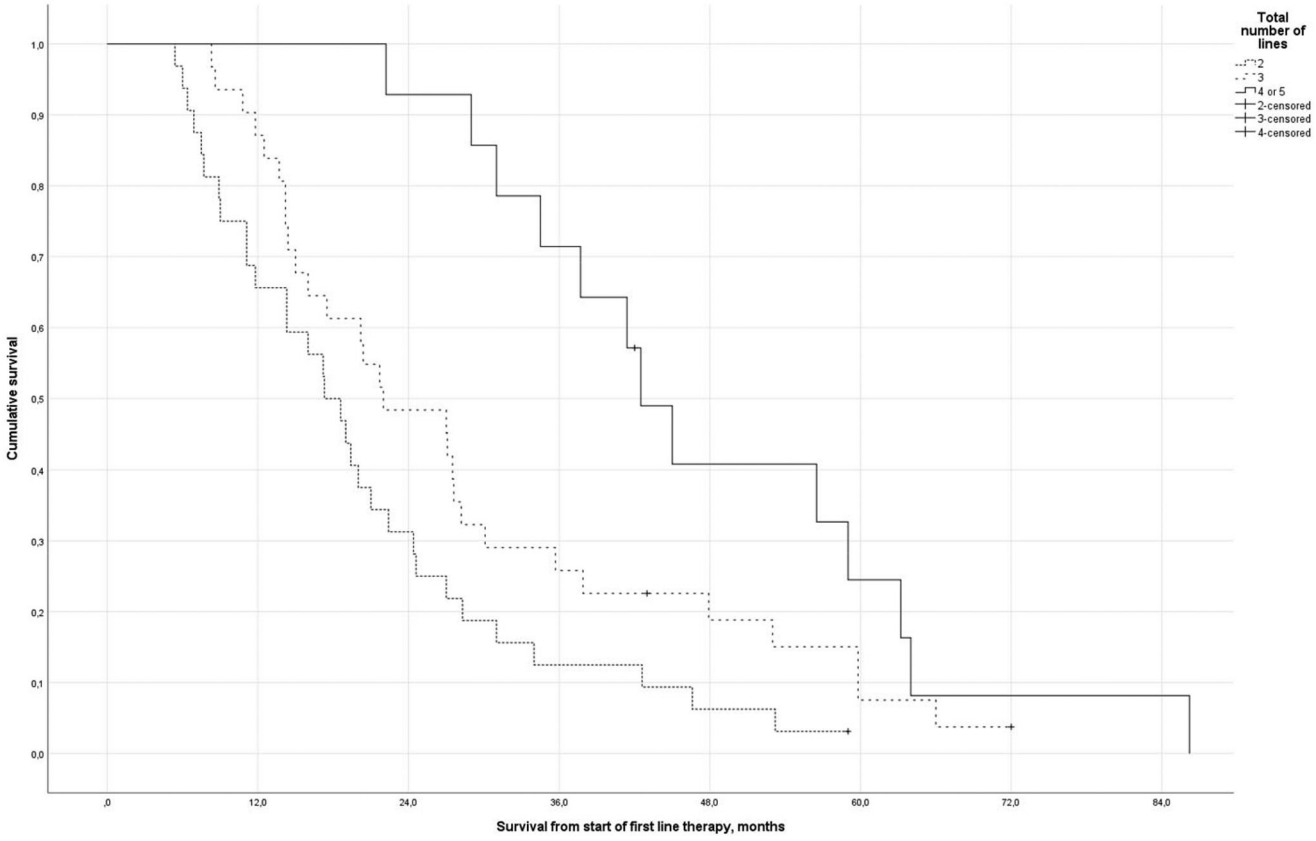

Figure 1. Actuarial Kaplan–Meier survival curves for patients treated with 2, 3 or more than 3 lines of systemic therapy. The median was 17.3, 22.0 and 42.5 months, respectively ($p < .05$ for all pairwise comparisons).

drugs essential for overall efficacy, and is there any preferable sequence of drugs in the first 2 lines? We found that a relevant proportion of patients (42%) were not eligible for treatment beyond second line and that advanced age (≥75 years) and not being able or willing to receive docetaxel as first or second-line therapy predicted for lower likelihood of treatment beyond second line. Ability to receive at least 3 lines was associated with better survival, and especially patients who received at least 4 lines had favorable median survival (42.5 months). Given that patients who progress and deteriorate rapidly are not eligible for further treatment, it is not surprising to see that those who maintain a good performance status and live longer despite continuous, but slow progression of disease eventually receive several different lines of treatment. In other words, there is a component of self-fulfilling prophecy in these patterns of treatment and survival outcomes, even if prospective clinical trials have shown that the 5 available drugs were able to prolong survival [1].

The multivariate analysis suggested that none of the drugs was essential to provide prolonged survival and that it was more important to receive as many sequential drugs as possible, than to adhere to one particular sequence in the first 2 lines. The slightly different survival results displayed in Table 2 must be interpreted with caution, because of the potential for significant bias and also the small group sizes. Typically, the physicians had good reasons to prefer one sequence over the others, such as presence of visceral metastases and rapid evolution of the disease (arguments in favor of chemotherapy), response/resistance to the previous line, or comorbidities, reduced performance status and geriatric issues. The relatively large PROXIMA study has shown that overall survival and progression-free survival did not differ significantly across different treatment modalities (circa 900 patients with MCRPC who experienced disease progression during or after docetaxel therapy) [5]. In the retrospective CATS trial, sequencing of docetaxel, cabazitaxel, and one endocrine therapy, was associated with median survival of up to 36 months [4]. Cabazitaxel seemed to retain its activity regardless of treatment sequence. Docetaxel activity after endocrine therapy appeared to be reduced, but the data were insufficient to conclude that cross-resistance occurs. The CARD investigators randomly assigned patients who had previously received docetaxel and an endocrine therapy (abiraterone acetate or enzalutamide) to receive cabazitaxel or the other androgen-signaling-targeted inhibitor in third line [11]. The median overall survival was 13.6 months with cabazitaxel and 11.0 months with the androgen-signaling-targeted inhibitor (hazard ratio 0.64, $p = .008$). However, many patients managed outside of clinical trials are unfit for 2 lines of chemotherapy, i.e. docetaxel and later cabazitaxel. In light of the recent approval of several drugs in settings earlier than MCRPC [12], additional challenges regarding future choice of sequence appear likely.

This study cohort consisted mainly of elderly, retired men (median age 69 years) with bone-only metastases. Typically, metastatic disease developed after an initial period of locally or locoregionally confined cancer. Travel distance was not

associated with undesirable disparities in receipt of sequential therapies. The Norwegian publicly-funded health care system provides free travel and accommodation to patients referred to specialist care (except for a minor share covered by the patients). Primary care is provided by each individual community (physicians responsible for general care and, if needed, referral to specialist care; home care provided by nurses and oncology nurses; nursing homes; rehabilitation; cancer care coordinator). Limitations of this study include the number of patients, statistical power of subgroup analyses and retrospective design. Due to already small subgroup sizes, we decided not to stratify further, e.g. by looking at different drug dosing regimens. In principle, weekly low-dose docetaxel may be inferior to higher doses administered every 3 weeks [13]. We also decided not to differentiate between treatment changes caused by toxicity and disease progression. Information about performance status and serum biomarkers that may influence survival was not available in our database. Possibly, patients with initial performance status of 2 may receive fewer lines of treatment than those with better performance status. A strength of this study is the completeness of data, ensured by the fact that the EPR also includes information from all local hospitals in the county. The absence of other oncology care providers further enhances the data quality.

We wanted to confirm that all patients in our region have equal access to sequential systemic therapy. Access to smaller and less specialized local hospitals, which can provide chemotherapy infusions and participate in video-streamed multidisciplinary tumor boards and virtual meetings with oncologists, provides a framework for quality care also in the most remote areas of our sparsely populated county. The present results confirm the efficacy of the regional structures and treatment pathways, and expand our previous findings by focusing on sequential therapies [14]. In other studies from different health care settings, geographical disparities and problems with rural health care have been identified [15–19]. While transfer of our current oncology care model to less well-served regions outside of Norway may be considered, the economic consequences and difficulties in recruiting qualified staff pose serious challenges. The fact that older patients often receive fewer lines of systemic cancer treatment is well known and mainly related to treatment safety in the presence of comorbidity and contraindications [20,21]. However, age alone should not be regarded a general barrier [22].

Conclusions

There was no indication toward under-treatment with systemic therapy among patients from the distant regions. Sequential treatment was feasible and survival increased with each additional line.

Ethical approval

As a retrospective quality of care analysis, no approval from the Regional Committee for Medical and Health Research Ethics (REK Nord) was necessary (national policy in Norway). This research project was carried out according to our institutions' guidelines and with permission to access the patients' data.

Author's contributions

CN participated in the design of the study and performed the statistical analysis. AD, EH and CN collected patient data. CN, EH and AD conceived of the study and drafted the manuscript. All authors read and approved the final manuscript.

Disclosure statement

The authors report no conflict of interest.

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Availability of data and materials

Data will not be shared, but a copy of relevant baseline parameters can be provided to researchers attempting to pool data from several institutions for large-scale analyses.

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