Costs of managing castrate-resistant metastatic prostate cancer patients at Inkosi Albert Luthuli Central Hospital

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Background: Metastatic castration-resistant prostate cancer (mCRPC) has a five-year survival rate of 30% despite the availability of expensive therapeutic agents. This study investigated the costs to a tertiary public hospital of the management of mCRPC with various therapeutic agents.

Methods: Between 1 January 2017 and 24 November 2019 the records of patients who were diagnosed with mCRPC and received chemotherapy (docetaxel) in combination with goserelin (a luteinising hormone-releasing hormone [LHRH]), or bicalutemide (an anti-androgen) at the Inkosi Albert Luthuli Central Hospital were analysed. The activity-based costing (ABC) model was used to calculate the medicine costs and other expenses incurred by the hospital.

Results: During the study period, 64 patients, mean age 66 years (± 8.7) at first visit, met the inclusion criteria of this study. The total cost incurred by the hospital was R10 338 559. On average, a total of R161 540 (SEM R22 699.00) per patient was incurred by the hospital. There was 60% reduction (p = 0.01), after the average period of 4 months (± 2.9), in PSA levels in patients who received goserelin monotherapy.

Conclusion: The therapeutic gain from extremely expensive therapy in mCRPC patients requires evaluation of clinical response and survival data to justify the expense.

Keywords: prostate cancer, prostate-specific antigen, chemotherapy, activity-based costing

Introduction

The South African Medical Research Council (SAMRC) reported that in 2012 cancer was the fifth leading cause of death in South Africa, causing 8.7% of all reported deaths.1 Prostate cancer (PCA) has the second highest frequency of all cancers, although local data is insufficient due to under-reporting of PCA cases in particular.2 Histologically adenocarcinoma accounts for 90% of cases PCA and occurs most commonly in men above 50 years of age. In South Africa, PCA is a leading organ-specific cancer in males, with 12 452 new cases diagnosed in 2018.3 The prostate-specific antigen (PSA) blood test and a digital rectal examination are the recommended screening tools for PCA, indicating the need for a prostate biopsy. The PSA level is further used to prognosticate and to guide the choice of appropriate management.3,4 Depending on their risk stratification, staging and grading of the PCA, patients are either placed on surveillance by means of ‘watchful waiting’ or ‘active surveillance’, or they are offered treatment. Curative treatment options include surgery (radical prostatectomy) and/or radiation therapy (external beam and/or brachytherapy).3,6 Patients with advanced or metastatic disease may be managed with a variety of treatments depending on several factors including the extent of disease, their comorbidities and functional status as well as hospital resources. Treatment options include hormonal agents (anti-androgens and LHRH agonists), chemotherapy (docetaxel), palliative radiation therapy and supportive care.7 The aim of these treatments, therefore, is to improve the progression-free survival and overall survival of patients in addition to improving their quality-of-life parameters.

The cost of treatment of PCA has been identified as the main driver of the economic burden due to this disease, globally.8,9 In South Africa, Heyns and colleagues reported that the use of bilateral orchietomy, as compared to androgen deprivation therapy (luteinising hormone-releasing hormone analogue [LHRHa] and/or bicalutamide) in patients diagnosed with advanced PCA, from January 1996 to December 2007, resulted in a saving of ZAR24 321 000.10 However, there have been no recent studies that have investigated the overall total costs associated with management of metastatic castrate-resistant prostate cancer (mCRPC) in South Africa. About 20% of PCA patients develop mCRPC within 5 years of hormonal ablation therapy.11 Therefore, this study investigated the overall costs incurred by a tertiary public hospital for the management of mCRPC with standard chemotherapy regimens.
Methods
This was a retrospective, descriptive study conducted on patients' electronic records at the Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa. IALCH is a public/private partnership tertiary/quaternary 840-bed hospital. Patients are referred from other hospitals in KwaZulu-Natal (KZN) province by telephonic/electronic booking systems. PCa patients are seen in a weekly combined urology-oncology clinic. New patient waiting time is approximately 3–6 weeks, with an average of 30–40 new patients monthly.

The files of patients who were diagnosed with metastatic PCa and had received chemotherapy in combination with goserelin and/or bicalutamide (at standard recommended doses) between 1 January 2017 and 24 November 2019 were identified. Patient data were extracted using the hospital’s MediTech™ paperless/electronic information technology (IT) system. The activity-based costing (ABC) model, as was validated at other similar settings, was utilised to calculate the cost incurred by the hospital. Briefly, this costing model sources data from various hospital information systems with various predetermined relationships and calculations. The direct costs would include medicines and laboratory investigations. Indirect costs are distributed to locations and services primarily by clinical volumes or cost drivers. For example, indirect costs include telephone and electricity bills, medical equipment, doctors, paramedical services such as physiotherapy, IT equipment, cleaning and porter services, patient registrations, human resource and financial services, as well as patient catering. In a ward, the activity that drives the cost is usually inpatient days. Therefore, the inpatient days or occupancy would be the cost driver.

Data were captured on Microsoft Excel, and GraphPad Prism programme was used for bivariate statistical analyses and to determine the quantitative measures of dependence (such as the Spearman’s r correlation). Statistical significance for categorical variables was tested using the chi-square test with Yates correction. Descriptive statistics for frequencies, means and standard deviations (SD) or standard error of the mean (SEM) error bars, medians and interquartile range (IQR), and 95% confidence intervals (CI) where applicable were used. Differences with p-values less than 0.05 were considered significant. Further, the Cohen’s d (and equation) was used to determine the effect sizes to inform clinical significance beyond the statistical significance which the p-values provide.

Results
Of the 327 patients with malignant neoplasm of the prostate, 64 received hormonal and/or chemotherapy for mCRPC. Their average age was 66 years (± 8.7) at first visit. The majority, 59% (n = 38), of patients where Black; 25% (n = 16), and 13% (n = 8) were Indians and Whites, respectively. There was also one Coloured patient as well as one patient whose race could not be determined from the records. At first visit, the PSA levels ranged from 0.01 to 1997.0 ng/ml with median levels of 19.06 ng/ml (IQR 1.4–160.2 ng/ml).

The total cost incurred by the hospital for management of 64 mCRPC patients during the period of this study was

| Table I: Hormonal therapy, chemotherapy and pain management medicines administered to patients |
|---------------------------------------------------------------|
| **Chemotherapy, hormonal therapy drugs/regimens and other medicines** | **n (%)** | **Mean age in years (SD)** | **Doses/cycles** | **Spearman’s r (p-values) of mean age of goserelin group vs others** |
| Goserelin | 40 (63%) | 63 (SD 7.5) | 140 | - |
| Bicalutamide | 27 (42%) | 66 (SD 7.6) | 107 | 0.3 (p = 0.18) |
| Docetaxel | 17 (27%) | 64 (SD 6.9) | 100 | 0.4 (p = 0.16) |
| Goserelin + bicalutamide + docetaxel | 7 (11%) | 66 (SD 8.5) | 94 | 0.3 (p = 0.54) |
| Cyproterone acetate | 6 (9%) | 65 (SD 5.4) | 14 | - |
| Vinorelbine | 1 | - | 12 | - |
| Other chemotherapy (vincristine, 5-fluoro-uracil, cisplatin, doxorubicin, daclomycin monotherapies) | 5 | 1 dose for each patient | |
| Paracetamol packs of 100s | 44 (69%) | 66 (SD 7.3) | 224 | - |
| Ibuprofen packs of 84s | 7 (11%) | 64 (SD 8.0) | 10 | - |
| Morphine | 18 (28%) | 64 (SD 8.0) | 36 | - |
| Amitriptyline packs of 28s | 12 (19%) | 63 (SD 7.8) | 22 | - |
| Amitriptyline + morphine | 6 (9%) | 64 (SD 7.5) | 27 packs of 28s + 27 doses | - |

| Table II: PSA levels in patients treated with main hormonal therapy and chemotherapy regimens |
|---------------------------------------------------------------|
| **Main chemotherapy and hormonal therapy regimens** | **n; mean age in years (SD)** | **Median PSA levels (at 1st visit) in ng/mL (IQR)** | **Median PSA change between last and 1st visits (IQR)** | **Mean period, in months (SD)** |
| Goserelin | 7; 72 (8.3) | 9.8 (0.5–176.8) | -5.9 (-67.0–0.14); p = 0.01; 60% ↓ | 4 (2.9) |
| Goserelin + bicalutamide | 12; 66 (8.5) | 11.2 (0.32–104.1) | -0.1 (-12.8–65.1); p = 0.05; 1% ↓ | 13 (8.8) |
| Goserelin + bicalutamide + docetaxel | 5; 68 (9.3) | 5.4 (1.8–59.7) | 45.6 (18.45–446.1); p > 0.05; 844% ↑ | 23 (12.5) |
| Docetaxel | 4; 62 (3.0) | 174.3 (59.7–962.9) | 8.1 (-91.7–169.5); p > 0.05; 5% ↑ | 7 (4.6) |
Sixty-three per cent (n = 40) of patients, were treated with goserelin alone or in combination with chemotherapy drugs, while 42% (n = 27) and 27% (n = 17) were treated with bicalutamide and docetaxel (as monotherapy or in combination with other chemotherapy drugs), respectively. As shown in Table I, only 10% (n = 7) of patients were treated with goserelin, bicalutamide and docetaxel. There were no significant (p > 0.05) correlations between patient age at first visit and the choice of chemotherapy regimens. For pain management, morphine was more likely to be used as monotherapy than in combination with amitriptyline (odds ratio [OR] 3.1; 95% CI 1.1–8.2; p < 0.03).

Although there was a 60% reduction (p < 0.01), after the average period of four months (SD 2.9), in PSA levels, median change of -5.7 ng/ml (IQR -67.0 to -0.14), with patients who received goserelin, the effect size was greater than 0.8 (Cohen’s d 1.03). Meaning, there were large variations among patients for this reduction to be clinically significant. The change in PSA levels in other groups (as shown in Table II) were inconclusive to be used as surrogate markers for assessing the effectiveness of chemotherapy. This was because there were insufficient records on mortality to reasonably assess the survival rates. Sixty-three per cent (n = 40) of patients were treated with radiotherapy in addition to chemotherapy.

**Discussion**

The findings of this study, which was the first to quantify the costs incurred by a primarily public hospital in South Africa, indicate that the management of patients with mCRPC is complex and very costly. There were no published studies for direct comparison with the findings of the current research. However, the reports on cost of management of mCRPC patients in other settings in South Africa and globally provide an opportunity for comparison. In Italy, the cost of drug treatment represented more than 77% of the economic burden of the management of mCRPC. Recent estimates of the cost of drug treatments of mCRPC in Canadian public healthcare settings indicated that the mean cost of mCRPC drug treatments over an average period of 28 months was $48 428 (1 CAD = 10.15 on 31 January 2020). Therefore, other management approaches have been explored in order to save costs. Also, the findings of Heyns and colleagues showed that treating mCRPC with surgical castration (bilateral orchiectomy) instead of androgen suppression therapy by assessing the therapeutic gain by evaluating clinical and biochemical response and survival data.

Patients who achieved a PSA decline of ≥ 50% had better survival than those who did not, regardless of treatment.

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**Conflict of interest**

The authors declare no conflict of interest.

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**Ethical approval**

The study proposal and subsequent annual re-certifications were approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Ref.: BE458/18); KwaZulu-Natal Department of Health as well all applicable authorities/head of departments at the IALCH.

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