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).[5,6] 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 orchiectomy, 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.[12] 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**	**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, dactinomycin 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)

R10 338 559.00 (this was equivalent to 544 134 USD; 1 USD = 19 ZAR on 31 January 2020). On average, a total of R161 540.00 (SEM R22 699.00) per patient was incurred by the hospital. In particular, the hospital incurred the average cost of R5 477.00 (SEM R889.00) for therapy cycle per patient.

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.[8] 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 $48 428 (1 CAD = 10.15 on 31 January 2020).[7] Therefore, other management approaches have been explored in order to save costs. Also, the findings of Heyns and colleagues showed that treating mCRPC with surgical castration (bilateral orchiectomy) instead of androgen suppression chemotherapy, at a tertiary academic and public hospital in South Africa, was associated with cost saving of over R35 000 per patient per year – with no significant difference in PSA levels and mortality at last follow-up.[10,13] The current study reported an average total expenditure of R161 540 (SEM R22 699) per mCRPC patients with 60% reduction ($p = 0.01$), after the average period of four months (± 2.9), in PSA levels in patients who received goserelin therapy.

The use of PSA levels for PCa screening purposes is more controversial than when used for prognosis and as a surrogate marker for the assessment of the effectiveness of therapy. Therefore, it is recommended that reliable estimation of clinically-significant changes in PSA levels requires follow-up for at least 2 years due to substantial physiological variation in serum PSA.[14] In contrast, the findings of this study indicate that even after 2 years of follow-up, the serum PSA levels were still exceedingly variable with IQRs of -91.7 to 169.5 and 18.45 to 446.1 ng/ml in mCRPC patients treated with docetaxel (for a mean period of 7 months) and a triple regimen therapy (goserelin + bicalutamide + docetaxel, for a mean period of 23 months), respectively. A PSA velocity (PSAV), which is a longitudinal assessment of PSA, instead of a single PSA measurement is recommended.[14] A PSAV decline of ≥ 50% is a more reliable predictor of survival regardless of treatment, instead of achievement of the nadir serum PSA level of 4 ng/ml.[15,16]

This study was based only on patients' electronic records and therefore, mortality and details of clinical assessments could not be retrieved. This has highlighted the need for a multidisciplinary, prospective and longitudinal follow-up study to justify the cost of this extremely expensive mCRPC 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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