Chemotherapy in patients with hormone resistant prostate cancer: analysis of benefits and efficacy at a public hospital of Brazil

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| Abstract

Purpose: *Chemotherapy* with docetaxel in hormone resistant prostate cancer improves overall survival (OS); we evaluated patients of a general public hospital in Santo André, SP, Brazil, treated with docetaxel as first line chemotherapy and afterwards with second line chemotherapy based on mitoxantrone. ***Objectives:*** To identify the effects of chemotherapy in Progression Free Survival (PFS) and Overall Survival (OS) of first and second line chemotherapy treatments. ***Materials and Methods:*** We reviewed the records for 49 patients who received chemotherapy in the setting of disease progression despite castration. We evaluated PFS and OS in first line setting, and pain control and PSA levels in second line. ***Results:*** Among 49 patients who received chemotherapy with docetaxel, the median PFS was 7 months and OS was 15 months. Only 10 patients received second line chemotherapy, 8 of them with mitoxantrone. It was not possible to evaluate OS or PFS for those patients, although 50% of them seemed to have benefitted in controlling their pain and none of them heve reduced their PSA levels. By Cox regression, only presence of visceral disease and Gleason above 8 correlated significantly with PFS, whereas no correlations were found with OS. ***Conclusion:*** In our hands Docetaxel as the first line chemotherapy option for patients with castrate resistant prostate cancer produced OS results similar to the literature. Without the use of new drugs that are not available in our public sector, the benefits of second line chemotherapy are uncertain.

| Keywords

Prostate Cancer; Chemotherapy; Docetaxel; Mitoxantrone; Palliative Treatment

| Introduction

Men with advanced prostate cancer are usually treated with androgen ablation therapy. Most men respond initially to hormonal treatment, but their disease evolves and becomes resistant to further hormonal therapy. Metastases, particularly to bone and lymph nodes, are frequent in men with hormone-refractory prostate cancer (HRPC). Men with HRPC frequently have pain and other symptoms leading to impairment of quality of life (QOL).[1,2]

Prostate cancer was considered resistant to chemotherapy until the mid-1990s, when mitoxantrone with prednisone (MP) was shown in a Canadian study to have a role in the palliative treatment of metastatic HRPC.[2] Men with HRPC experienced an improvement in pain and QOL if treated with MP compared with prednisone alone. No survival benefit, however, was detected in trials comparing mitoxantrone plus corticosteroids with corticosteroids alone, although the studies were not powered to detect small differences in survival.[1,2,3]

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In 2004, reports of the TAX 327 and Southwest Oncology Group 99-16 studies showed significant survival benefit when docetaxel-based treatment was compared with mitoxantrone for men with metastatic HRPC. The TAX 327 study randomly assigned 1,006 men with metastatic HRPC to receive docetaxel 75 mg/m^2 administered every 3 weeks, docetaxel 30 mg/m^2 administered weekly for 5 of 6 weeks, or mitoxantrone 12 mg/m^2 every 3 weeks, each with prednisone 5 mg twice daily. The study showed significantly longer survival for the three weekly arm compared with the mitoxantrone one. [1,4]

In our study, we evaluated the characteristics of patients who received chemotherapy at a reference hospital of Santo André, SP, Brazil as first line or second line treatment, as well if there was any benefit in pain control. We also report on their Progression Free Survival (PFS) and Overall Survival (OS). Regarding second line treatment, our objective was to evaluate if there was any benefit for that population in terms of PSA and pain control, especially because newer and more expensive drugs are not available in the Brazilian Public Health System for HRPC, as cabazitaxel, abiraterone or enzalutamide.

| Materials and methods

This is a retrospective uni-institutional study that evaluated patients with HRPC treated with chemotherapy, at Mário Covas Hospital, Santo André, Brazil, between January 2010 and June 2013.

The patients were evaluated according to PSA levels and reducing, Gleason Score, previous treatment, chemotherapy, presence of visceral disease, Karnofsky Performance Status (KPS), treatment response, motives to stop treatment. Pain improvement and PSA reductions were evaluated in the patients submitted to second line chemotherapy.

We considered as treatment response a reduction superior to 50% of PSA levels, pain improvement as reported by the patient (no formal pain score) and radiologic response according to what was documented in the patients' files. Progression was defined as elevation of PSA and/or clinical or radiological worsening. All treatments were given according to Institutional Protocols based on the literature[4,5]

We analyzed overall survival (OS) defined as the date of the beginning of chemotherapy until death or loss of follow up, and progression free survival (PFS) as the date of the beginning of chemotherapy until the moment of disease progression. We used the Cox proportional hazards model for multivariate analysis using OS and PFS as dependent variables. We employed Log-Rank test to compare Kaplan-Meier curves to depict patients' OS and PFS. To test the significance of the association between categorical variables we employed the Fisher exact test. We considered as statistically significant p values of less than 0.05. We employed the SPSS package for all statistical calculations.

| Results

We included 49 consecutive patients with HRPC who received first line chemotherapy between January 2010 and June 2013. Forty-eight (98%) patients received docetaxel and only one (2%) received cisplatin and etoposide as first line treatment. Patient's clinical characteristics before the treatment are shown in Table 1.

Table 1. Patient's clinical and pathological characteristics at first line chemotherapy

		N (%)	
Age (years)	Media	72,2	
	Median	73,0	
	minimum-maximum	53,0-89,0	
	Standard Deviation	8,0	
First Line Chemotherapy	Docetaxel	48	98,0%
	Cisplatin and Etoposide	1	2,0%
Bone disease	Present	44	89,8%
	Absent	5	10,2%
Visceral disease	Present	7	14,3%
	absent	42	85,7%
Gleason Score	<7	18	36,7%
	8-10	27	55,1%
	Not available	4	8,2%
First treatment	Prostatectomy	12	24,5%
	Radiotherapy	8	16,3%
	Hormone therapy	29	59,2%
Hormone treatments	1	18	36,7%
	2	16	32,7%
	>2	15	30,6%
KPS	<70%	9	18,4%
	>70%	40	81,6%
	Total	49	100,0%
PSA	>20	34	69,4%
	<20	15	30,6%
	Total	49	100,0%

The reasons for patients to stop first line treatment are listed on table 2.

Table 2. Motives to stop first line chemotherapy

Motives to stop treatment		
Completed treatment	22	44,9%
Disease progression	15	30,6%
Adverse effect	4	8,2%
Death	5	10,2%
Others	3	6,1%
Total	49	100,0%

Patients that received docetaxel have 54% of reduction in the PSA levels and 66% have had their pain improved. The results on PSA and pain control from the 49 patients who received first line chemotherapy are showed in the table 3.

Table 3. PSA reduction and pain improvement after first line chemotherapy

	Kind of chemotherapy at 1st line			
	Docetaxel		**Cisplatin/Etoposide**	
	N		**N**	
PSA reduction				
Yes	22	45,8%	1	100,0%
No	26	54,2%	-	-
Total	48	100,0%	1	100,0%
Pain improvement				
Yes	32	66,7%	1	100,0%
No	16	33,3%	-	-
Total	48	100,0%	1	100,0%

Of these 49 patients, only 10 received second line chemotherapy. Eight patients received mitoxantrone, one received docetaxel and one received paclitaxel. Of those 10 patients, 6 finished treatment, 1 had disease progression, 1 presented severe side effects and 2 stopped treatment for other reasons (not reported).

After second line chemotherapy, seven (70%) patients had KPS reduction and 3 showed the same KPS of the beginning of the treatment. The reduction in KPS of these 7 patients varied from 10% to 30%. None of those patients had a 50% PSA reduction but 5 of them had pain improvement after second line chemotherapy. Ultimately, all patients progressed and 8 died.

Table 4 list those results regarding the second line treatment.

Table 4. PSA reduction and pain improvement after second line treatment

	Kind of chemotherapy in 2nd line					
	Docetaxel		**Mitoxantrone**		**Paclitaxel**	
	N		**N**		**N**	
PSA reduction						
Yes	-	-	-	-	-	-
No (%)	1	100,0%	8	100,0%	1	100,0%
Total	1	100,0%	8	100,0%	1	100,0%
Pain improvement						
Yes	-	-	4	50,0%	1	100,0%
No (%)	1	100,0%	4	50,0%	-	-
Total	1	100,0%	8	100,0%	1	100,0%

The OS for patients that had visceral metastases was 8,5 months and no visceral metastases was 22 months (p=0,013) and PFS for patients that had visceral metastases was 3 months and no visceral metastases was 9 months (p=0,013). The Gleason Score above 8 was also significantly correlated with PFS by Cox regression (p = 0.026). PSA levels and age did not correlate with either PFS or OS by Cox regression analysis, and Gleason score above 8 also did not correlate with OS.

Figure 1 and 2 show the Kaplan-Meier curves of OS and PFS regarding presence or not of visceral disease.

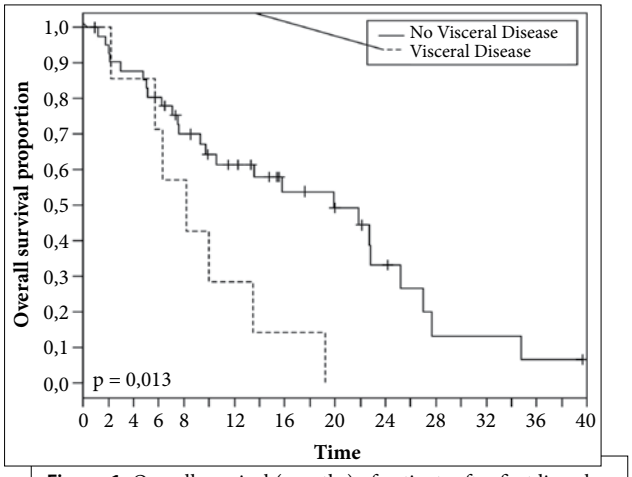

Figure 1. Overall survival (months) of patients after first line chemotherapy, according to the presence of visceral disease.

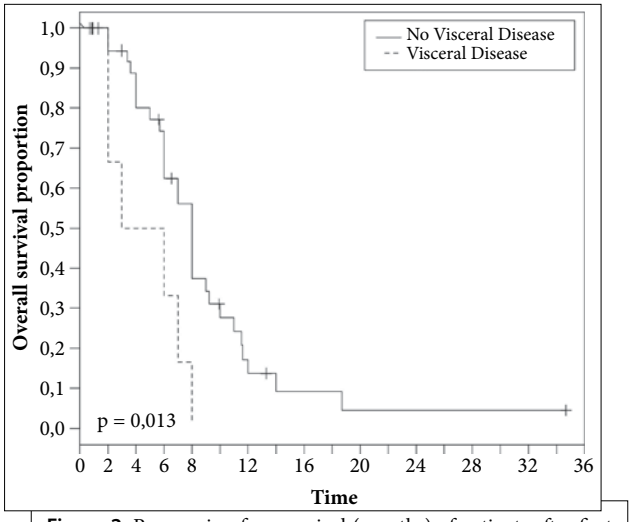

Figure 2. Progression free survival (months) of patients after first line chemotherapy, according to the presence of visceral disease.

| Discussion

The characteristics of the patients in this study are typical of those seen in oncology practices. Most patients were elderly and had received at least two types of hormonal manipulation. Most had bone metastases and a high serum PSA level, and about half had substantial pain. [6,7]

In TAX-327, the PSA reduction was 48% for the 3 weeks group and 48% for the group that received docetaxel weekly. The pain improvement was 35% and 31% respectively.[1,4] . In our study, we had a PSA reduction in 45% of patients who received docetaxel in first line. In 66% of patients, we have seen pain improvement. That´s superior to data of docetaxel studies, what can be related to the fact of being a retrospective study in which pain improvement was evaluated based in information written in files and we didn´t use a formal pain score.

In our study we found a median OS of 15 months whereas In TAX-327 the median OS was of 18 months for patients who received docetaxel every 3 weeks. In our study also, we retrospectively study an underserved population of patients, many of whom with comorbidities. Those factors may explain the lower survival of our study[8]. Furthermore, we have observed a tendency to dose reduction in the files we evaluated in order to minimize toxicities, which can have interfered with our results as well.

We found a statistically difference in the OS and PFS in patients with visceral metastases comparing with no visceral metastases, as expected for this population, besides the small number of subjects in this group (14% of 49 patients)[9].

We do not have in our service any medications approved for second line treatment of patients who had a progression after docetaxel, such as cabazitaxel[9,10], abiraterone[11] or enzalutamide[12]. Therefore, we used mitoxantrone in the majority of cases in this setting. Only ten patients have received second line therapy, maybe because the poor KPS after progression on first line treatment.

Despite the small population treated in our study, we did not have PSA reduction for those who received mitoxantrone as second line treatment, and 50% of patients had pain improvement. However, in 70% of these cases we noted a reduction of KPS, which brings the question of the real benefit of offering this treatment after first line.

| Conclusion

We conclude that our results after first line docetaxel chemotherapy for HRPC are in line with the literature, specially accounting for a less selected population of patients and with worse social and economic conditions that we included in our study.

New drugs such as abiraterone, enzalutamide and cabazitaxel would be available for our public patients for second line therapy if we hope to increase their survival and quality of life.

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