Multiple Rechallenges for Castration-resistant Prostate Cancer Patients Responding to First-line Docetaxel: Assessment of Clinical Outcomes and Predictive Factors

Orazio Caffo, Giovanni Pappagallo, Sonia Brugnara, Alessia Caldara, Maria Chiara di Pasquale, Antonella Ferro, Michela Frisinghelli, Viviana Murgia, Lucianna Maria Russo, Barbara Soini, Francesco Valduga, Antonello Veccia, and Enzo Galligioni

OBJECTIVE To describe the feasibility and efficacy of multiple sequential rechallenges and analyze the predictive factors that may aid in selecting patients who are more likely to respond. Several studies have demonstrated the feasibility and activity of a single docetaxel rechallenge in patients with castration-resistant prostate cancer (CRPC), thus providing an additional opportunity for treatment in docetaxel-sensitive CRPC patients in clinical practice.

MATERIALS AND METHODS CRPC patients who completed first-line docetaxel therapy without disease progression have been offered a docetaxel rechallenge, and the responders have undergone further rechallenges until the appearance of docetaxel resistance. We assessed their clinical outcomes and evaluated all the variables potentially capable of predicting the response to rechallenge by means of uni- and multivariate analysis.

RESULTS Forty-six consecutive patients underwent 92 rechallenges. The overall biochemical response rate (prostate-specific antigen [PSA] reduction >50%) was 66%. Median overall survival was 32 months with a projected 2-year overall survival from the first docetaxel administration of 77.5%. Multivariate analysis showed that the time slope-log PSA, the time from the previous cycle, and the response to the previous cycle were predictive of the response to a rechallenge.

CONCLUSION A docetaxel rechallenge may be safely repeated several times in CRPC patients and in selected patients could improve disease control. The predictive factors found in our analysis may help select the most appropriate strategy in the light of the availability of active second-line drugs. UROLOGY 79: 644–649, 2012. © 2012 Elsevier Inc.

Docetaxel-based chemotherapy is currently the treatment of choice for patients with castration-resistant prostate cancer (CRPC) because it prolongs their survival compared with previously standard mitoxantrone therapy.[1,2] The protocol of the TAX327 trial was completed by 35% of the patients receiving the planned courses of treatment in the weekly arm, and 46% of those in the 3-weekly arm. This reflects the findings of clinical practice in which some patients respond to docetaxel and discontinue treatment after receiving the planned (usually 8-10) courses of therapy without experiencing disease progression. The docetaxel-sensitivity profile of these patients is clearly different from that of those who stop first-line treatment because of disease progression, but all of them will have disease progression some time after the discontinuation of docetaxel: in the SWOG trial the time to progression was 6.3 months,[2] and in the winning arm of the TAX327 trial, the prostate-specific antigen (PSA) response duration was 7.7 months.[1] The question is whether these patients are still sensitive to docetaxel: in other words, whether it is possible to repeat docetaxel-based treatment and achieve a new response that significantly prolongs disease control.

In the absence of an active second-line treatment, several studies have demonstrated the feasibility and ac-

From the Department of Medical Oncology, Santa Chiara Hospital, Trento, Italy; and Epidemiology and Clinical, Trials Office, Oncology and Hematology Unit, Mirano, Italy

Reprint requests: Orazio Caffo, M.D., Medical Oncology Department, Santa Chiara Hospital, Largo Medaglie d'Oro, 38100 Trento, Italy. E-mail: orazio.caffo@apss.tn.it

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tivity of a single docetaxel rechallenge,[3-5] thus providing an additional opportunity for treatment in docetaxel-sensitive CRPC patients in clinical practice. It has been observed that the time between the end of first-line therapy and the start of a rechallenge predicts the activity of the repeated treatment.[4]

The aim of this paper is to describe the feasibility and efficacy of multiple sequential rechallenges in docetaxel-sensitive CRPC patients, and to analyze the predictive factors that may help in selecting patients who are more likely to respond.

MATERIAL AND METHODS

Since 2002, all of the CRPC patients attending our department have been offered first-line therapy with docetaxel-based therapies: docetaxel alone or docetaxel plus estramustine administered using either a 3-weekly or weekly schedule. The patients who completed the planned treatment without experiencing disease progression were considered docetaxel sensitive and, at the time of subsequent disease progression, those with an adequate performance status were given the opportunity to repeat docetaxel-based chemotherapy. The rechallenge usually adopted the same schedule as that previously used, except in the case of patients who received the 3-week docetaxel schedule and experienced major toxicity, or whose performance status worsened during the treatment holiday; these patients were offered a weekly docetaxel schedule. During the rechallenge, we usually proposed no more than 4-6 courses.

After the first rechallenge, the responders continued to be considered docetaxel-sensitive and capable of undergoing further rechallenges unless contraindications appeared during the treatment holiday (eg, an inadequate performance status, new comorbidities) or they had experienced unacceptable toxicities during the rechallenge. Subsequent rechallenges were proposed until the appearance of real docetaxel resistance, ie, disease progression during docetaxel treatment.

Disease progression during first-line treatment, the treatment holidays and the rechallenges was defined on the basis of the recommendations of the Prostate Cancer Clinical Trials Working Group.[6] However, because patient management was mainly oriented towards everyday clinical practice, the patients only underwent instrumental restaging if it was clinically indicated and the dynamics of PSA were closely monitored (before each docetaxel administration and every two months during treatment holidays). In the case of a >25% increase in PSA levels, 2 independent measurements were made separated by a two-week interval.

All the patients gave their written informed consent to receive docetaxel rechallenges.

For the purposes of this study, we recorded the main findings in the patients' prostate cancer histories. For each rechallenge course, these included: (1) The type and schedule of treatment (the addition of estramustine and timing); (2) the response to chemotherapy in accordance with the guidelines of the Prostate-Specific Antigen Working Group[6] (3) toxicity in accordance with the NCIC Common Terminology Criteria, version 3.0; (4) PSA values during treatment; (5) PSA values during the previous treatment holiday; (6) time since the previous chemotherapy; and (7) baseline prognostic variables (hemoglobin and alkaline phosphatase levels, the presence of pain, and ECOG performance status).

Table 1. Patient characteristics

No. of Patients	46
Age (y)	
Median	70
Range	57-82
Time from diagnosis of primary cancer (mo)	
Median	38.5
Range	8-159
Gleason score	
Median	8
Range	5-10
Primary local treatment	
Prostatectomy	5
Radiotherapy	6
None	35
Number of hormonal treatments	
Median	2
Range	2-5
Previous docetaxel treatment schedule	
Every 3 weeks	40
Weekly	6
Disease extension at baseline	
Bone metastases	45
Liver metastases	1
Nodal metastases	9

Quality of life was recorded by QLQ-C30 questionnaire, which was administered at the start and at the end of the docetaxel courses.

Statistical Considerations

The continuous variables are given as median values and interquartile ranges (IQRs), and the discrete variables as relative frequencies and 95% confidence intervals. Overall survival (OS) was calculated from the start of first-line docetaxel therapy to death using the Kaplan-Meier method, and is given as median values and 95% CIs. The following variables were considered as being potentially capable of predicting a response to a rechallenge: treatment schedule (3-weekly vs weekly), estramustine administration (yes vs no), PSA response to the previous docetaxel course (a 50% reduction in comparison with baseline, yes vs no), baseline parameters (hemoglobin and alkaline phosphatase levels, the presence of pain, ECOG performance status), the number of previous docetaxel courses, PSA parameters (slope log, doubling time and velocity) previous docetaxel course and treatment holiday, and the duration of the treatment holiday before a rechallenge. The PSA parameters were calculated online at the website of MSKCC (http://www.mskcc.org) and analyzed by means of binary logistic regression. The continuous variables were categorized by quartiles and chosen for the initial model after a univariate chi-square analysis.

RESULTS

Between January 2002 and December 2010, 46 patients were considered docetaxel-sensitive because they responded to docetaxel-based first-line chemotherapy and discontinued the treatment without experiencing disease progression. All of these patients underwent at least one docetaxel rechallenge, and Table 1 shows their characteristics at the beginning of the first rechallenge.

Table 2. Main findings of rechallenges

	Responders (PSA reduction >50%)	Nonresponders
Number of rechallenges	63	29
Rechallenges sequence		
1st rechallenge	31	15
2nd rechallenge	17	10
3rd rechallenge	7	1
4th rechallenge	5	0
5th rechallenge	3	1
6th rechallenge	0	1
7th rechallenge	0	1
Schedule		
DOC/3 wks	4	5
DOC+E/3 wks	34	15
DOC weekly	2	1
DOC+E weekly	23	8
Baseline hemoglobin levels (g/dl)		
Median	13.1	12.3
Range	9.0-16.5	7.0-15.6
Baseline alkaline phosphatase levels (IU/L)		
Median	88	103
Range	50-1163	56-3048
Pain		
Yes	17	5
No	46	24
ECOG PS		
Median	0	0
Range	0-2	0-2
Time from previous DOC (weeks)		
Median	24	19
Range	5-100	13-67
PSA parameters during previous treatment		
Median log slope	−0.58	−0.33
Median doubling time	−1.15	−2.22
Median velocity	−12.72	−11.98
PSA parameters during previous holiday		
Median log slope	0.535	0.41
Median doubling time	1.29	1.69
Median velocity	21.13	11.38

DOC = docetaxel; E = estramustine phosphate; PS = performance status; PSA = prostate specific antigen.

Nineteen patients underwent one rechallenge, 19 underwent two, 3 underwent three, 1 underwent four, 3 underwent five, and 1 underwent seven. Twenty patients can still be considered docetaxel-sensitive and potentially capable of undergoing further rechallenges in the future.

Clinical Outcomes

We recorded the data relating to a total of 92 rechallenges, the main features of which are shown in Table 2. Each rechallenge involved a median of 4 docetaxel administrations (range 1-9): in 7 cases, docetaxel was continued after the sixth administration as a result of good patient compliance and the reduction in PSA levels.

Figure 1 shows the biochemical responses in the rechallenges as a whole. The overall biochemical response rate (a >50% reduction in PSA levels) was 66% (95% CI 56-76).

The treatments were well tolerated and led to a very limited number of major toxicities: 1 patient developed grade 3 anemia (2%), 1 grade 3 neutropenia (2%), and 1 grade 3 sensitive neuropathy (2%); 2 patients developed deep vein thrombosis (4%) but continued treatment combined with antithrombotic therapy. No patient had to stop a rechallenge because of toxicity, and there no treatment-related deaths. No changes were observed in terms of QLQ-C30 outcomes, excepting for pain improvement in patients who have been symptomatic at baseline.

After a median follow-up of 25 months, 20 patients are still alive and 26 have died. The median OS in the patients as a whole was 32 months from the start of first-line therapy (95% CI 25-39), and 18 months from the start of the first rechallenge (95% CI 13-23); the projected 2-year OS from the first docetaxel administration was 77.5% (95% CI 64.4-90.5). Considering only the patients undergoing at least 2 rechallenges, median OS was 40 months (95% CI 32-48) from the start of first-line therapy, and 22 months (95% CI 17-27) from the start of the first rechallenge start; the projected 2-year OS from the first docetaxel administration 88.4% (95% CI 75-100).

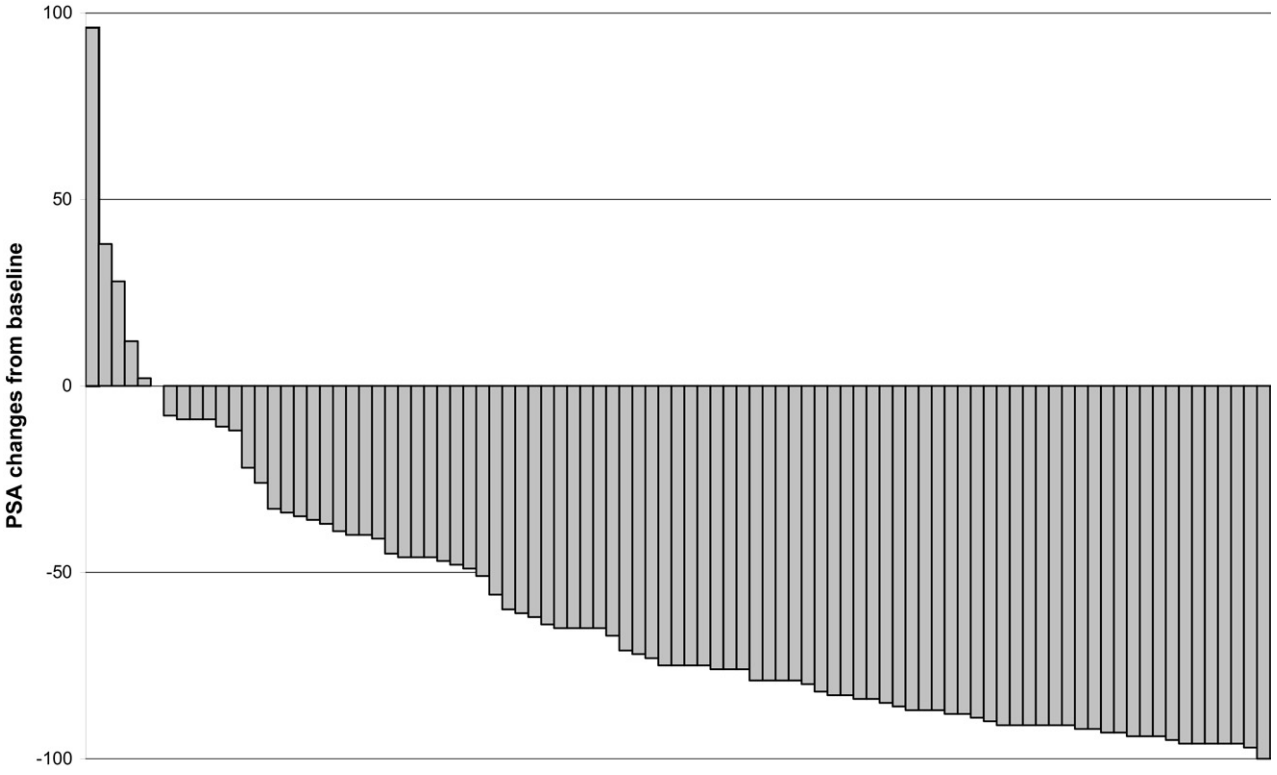

Figure 1. Waterfall plot of biochemical responses at rechallenges.

Table 3. Assessment of predictive factors

	Univariate Analysis		Multivariate Analysis	
Variable	Pearson χ^2	*P* Value	Exp (Beta)	*P* Value
Schedule timing	1.081	.298		
Estramustine addition	0.486	.486		
Biochemical response during the previous chemotherapy course	8.192	.004	7.658	.014
PSA doubling time (during the previous chemotherapy course)	3.941	.047	1.334	.687
PSA velocity (during the previous chemotherapy course)	0.778	.484		
Log PSA (during the previous chemotherapy course)	2.964	.085		
PSA doubling time (during the previous treatment holiday)	2.616	.106		
PSA velocity (during the previous treatment holiday)	0.585	.380		
Log PSA (during the previous treatment holiday)	5.042	.025	8.965	.020
Time since the previous chemotherapy	5.712	.017	8.212	.002
Baseline hemoglobin level	2.267	.132		
Baseline alkaline phosphatase level	0.461	.497		
Baseline presence of pain	0.768	.506		
Baseline ECOG performance status	2.565	.109		
Number of previous docetaxel courses	0.134	.714		

Assessment of Predictive Factors

Univariate analysis showed that PSA response to the previous docetaxel course, the duration of the preceding treatment holiday (≥23 weeks), PSA doubling time during the previous docetaxel course, and the slope-log PSA ≥0.62 during the preceding treatment holiday were predictive of a rechallenge response (Table 3), whereas multivariate analysis showed that only interval slope-log PSA, the duration of the preceding treatment holiday, and the response to the previous cycle confirmed their predictive value.

We used these factors to obtain a predictive score by assigning one point to each when it was present before the start of the rechallenge; the rechallenges with baseline scores of 3, 2, and 0-1 led to biochemical response rates of respectively 100%, 86%, and 32.3%.

COMMENT

To the best of our knowledge, this is the first study demonstrating the feasibility and activity of sequential multiple docetaxel rechallenges in patients with CRPC

and providing additional information concerning the predictive variables capable of identifying those who are more likely to respond to a rechallenge.

The scenario of CRPC treatment has changed since it was first demonstrated that docetaxel can prolong patient survival.[1,2] However, the possibility of proposing second-line treatment was limited by the discouraging results obtained with mitoxantrone: biochemical disease control of 6-20%.[7-10] Two large-scale randomized phase III trials have recently tested the efficacy of new drugs as second-line treatment after docetaxel failure: cabazitaxel, a new taxane that led to better survival than mitoxantrone,[11] and abiraterone, a new CYP17 inhibitor that was superior to placebo in terms of survival.[12] Unfortunately, to date these drugs are not available in clinical practice.

In this context, the use of a docetaxel rechallenge has been viewed as a possible option for patients responding to first-line docetaxel who discontinue treatment without experiencing disease progression. The rationale for a rechallenge is related to the possibility of obtaining a new response by retreating patients with the same drug to which they have previously responded. This strategy has to be clearly distinguished from that involving second-line treatment with a combination of docetaxel and a second drug in the hope of overcoming docetaxel resistance.[13-15]

Excluding one study of a very small sample of patients,[16] the first study of a docetaxel rechallenge in CRPC patients was published by Eymard et al,[3] who retrospectively reviewed a series of 50 patients (48% of whom had undergone rechallenge as third- or fourth-line treatment) and found a biochemical response rate of 48% with manageable toxicity. There are a number of differences between this study and ours: we used multiple rechallenges instead of a single rechallenge; a limited number of cycles instead of treatment until progression for each rechallenge (except in a very few cases); and rechallenge only after a first-line failure instead of multiple-line failure. There are also a number of differences in the results: we observed grades 3-4 hematological toxicity in 2% of the patients (vs 6% in Eymard study), a median survival from the start of rechallenge start of 18 months (vs 16 months), and a 2-year overall survival rate of 77.5% (vs 28.9%). Another French retrospective study involved a series of 39 patients and again docetaxel rechallenge was proposed once, and frequently (in 74% of the patients) as a third or further treatment line.[4] As a result, the biochemical response rate (defined as a >50% reduction in PSA levels) was only 38%, with median survival after the rechallenge of 15.8 months.

The first prospective study of a rechallenge was published by Di Lorenzo et al,[5] who chose an arbitrary 5-month cut-off period before proposing the rechallenge to patients who had not progressed during first-line docetaxel. The rechallenge was limited to a single course and was not proposed again in the case of a new response to treatment. It was also continued until progression, which may explain the toxicity profile (24.5% grades 3-4 neutropenia and 11.1% grades 3-4 thrombocytopenia). Furthermore, only 24.5% of the patients experienced a 50% reduction in PSA levels.

Our experience not only confirms that a rechallenge after first-line docetaxel discontinuation is feasible and safe, but also demonstrated that a rechallenge may be repeated several times with a good toxicity profile and good disease control. We proposed no more than 4-6 courses during each rechallenge in the hope of improving patient compliance, reducing the burden of toxicity, maintaining bone marrow function, and preserving the patients' quality of life. It is worth noting that the incidence of common docetaxel-related side effects was very limited: neuropathy was mild (grade 3 in only one rechallenge and grade 1 in another), and there was no case of tearing eyes. This may also explain the lower incidence of major hematological toxicities than in the previously published studies of rechallenges. In our experience, the biochemical response rate was higher than those previously reported and the rechallenges led to a response regardless of whether the 3-weekly or weekly schedule was used. Furthermore, the need to modify the treatment schedule because of a change in performance status did not reduce potential drug activity: a weekly schedule administered to a patient who had previously received the 3-week schedule had the same probability of achieving a response as the previous schedule.

In our strategy, a rechallenge may be proposed in the absence of contraindications (such as a worsened performance status or the onset of comorbidities) until the development of resistance to docetaxel, ie, disease progression during treatment. In terms of results, clinical outcomes in our series were better than those observed in previous studies.

Given the forthcoming availability of active second-line drugs in and the promising clinical outcomes of docetaxel rechallenges, it is essential to be able to select the patients who are most likely to respond to a rechallenge and those for whom a new drug may be more appropriate. We evaluated all the variables that may be predictive, including the parameters that have prognostic value in a recently developed model for CRPC patients undergoing chemotherapy,[17] and identified 3: the response to the previous docetaxel course, the duration of the previous treatment-free period, and the PSA-log during the same period. The first variable is strictly related to the rationale of a rechallenge: patients responding to the previous docetaxel course (on the basis of the recommendations of Prostate Cancer Clinical Trials Working Group[6]) are more likely to respond to a rechallenge.

The second predictive variable is the time free from progression after the completion of first-line therapy. This is also considered a predictive variable in other cancers: patients with ovarian cancer are considered sensitive to platinum if no progression is observed for at least 6 months,[18] and in small-cell lung cancer, the cut-off

time is 3 months.[19] In the case of CRPC, a previous study of a series of patients treated with a single rechallenge suggested an arbitrary cut-off period 5 months as a means of identifying the patients who are sensitive or resistant to docetaxel,[5] and Loriot et al[4] found that an interval of more than 3 months from the previous docetaxel course was associated with prolonged progression-free and OS. However, these authors did not assess further variables and did not specify the criteria defining these cut-off times. Our data confirm that the treatment-free interval predicts the response not only to a single rechallenge, but also to multiple rechallenges.

The third factor predictive of a rechallenge response was the PSA-log during the treatment-free interval calculated using the MSKCC formula. We evaluated all the variables of the MSKCC nomogram in terms of the trend of PSA levels during a treatment holiday (doubling time, velocity, and log) and found that the first 2 were not predictive even though they are more intuitively related to disease evolution, whereas log retained its statistical significance in the multivariate analysis. In our opinion, this observation may be valuable when it comes to selecting patients for a rechallenge because it is a parameter that can be monitored simply.

Given the clear differences in biochemical response rates between the patients with different predictive scores, it seems to be reasonable to propose a rechallenge when at least 2 predictive factors are present at the time of progression; otherwise, a true second-line treatment would appear to be a better choice.

Our study clearly has several limitations. First, it was based on a therapeutic strategy applied in clinical practice in the absence of active second-line therapy. Therefore, there is a lack of regular instrumental restaging and the choice of repeating treatment was related mainly to the trend of PSA levels. Furthermore, the decision to repeat docetaxel was not preplanned on the basis of a given PSA value, but was mainly a result of trend, recovery from the toxicity of the previous docetaxel course, and the patient's performance status and preference. By contrast, and for the same reasons, our results and conclusions may be considered user-friendly in the everyday management of CRPC patients. Second, our experience described a highly selected sample of patients who showed a prolonged sensitivity to docetaxel: it is clear that the rechallenge strategy may be not applied to the docetaxel failures.

In conclusion, although the strategy of a docetaxel rechallenge for CRPC was developed simply to cover the practical clinical need of what to do when fit patients progress after the discontinuation of first-line therapy, our study demonstrates that it may be safely repeated several times and can lead to a prolonged disease control. The predictive factors found in our analysis may be of help in choosing the most appropriate strategy in the light of the availability of active second-line drugs.

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