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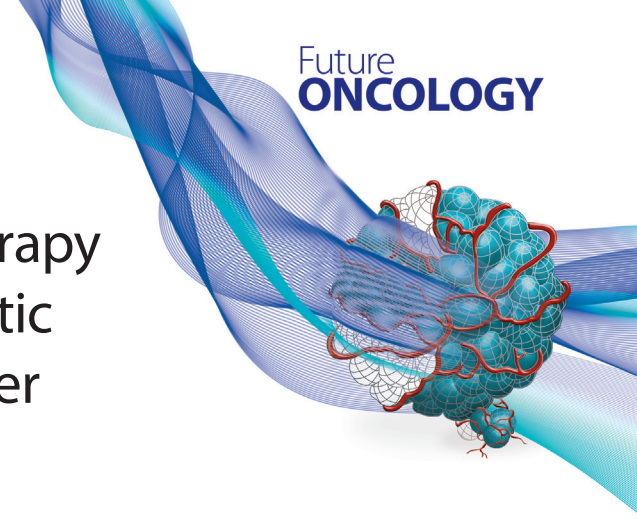

RESEARCH ARTICLE

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Intermittent docetaxel chemotherapy as first-line treatment for metastatic castration-resistant prostate cancer patients

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ABSTRACT **Aims:** The intermittent administration of chemotherapy is a means of preserving patients' quality of life (QL). The aim of this study was to verify whether the intermittent administration of docetaxel (DOC) improves the patients' QL. **Patients & methods:** All patients received DOC 70 mg/m^2 every 3 weeks for eight cycles. The patients were randomized to receive DOC continuously or with a fixed 3-month interval after the first four DOC courses. **Results:** The study involved 148 patients. There was no difference in QL between the groups receiving intermittent or continuous treatment. Intermittence had no detrimental effects on disease control. **Conclusion:** Although feasible and not detrimental, our results showed that true intermittent chemotherapy in metastatic castration-resistant prostate cancer patients failed to improve the patients' QL.

KEYWORDS
• castration-resistant prostate cancer • docetaxel • intermittent chemotherapy • quality of life • randomized trial

Since the demonstration of a survival advantage over mitoxantrone [1,2], docetaxel (DOC) has become the drug of choice for the first-line treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). In the pivotal trial, the patients received ten DOC courses and it has recently been demonstrated that patients responding to treatment do not have any advantage in receiving more than ten DOC courses [3]: these findings supported the clinical practice of administering eight to ten DOC courses. Although DOC-based treatments have improved (or at least have not worsened) the patients' quality of life (QL) [1,4–5], there is a common feeling in everyday clinical practice that some patients may experience the cumulative burden of side effects during treatment.

One possible means of improving the patients' QL is to administer intermittent rather than continuous chemotherapy, as has been tested in patients with metastatic breast cancer [6–9] and metastatic

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colorectal cancer [10–13]. Although these studies led to conflicting results in terms of the differences in QL and disease control between the intermittent and continuous strategies, they did provide evidence that a response can still be obtained when the treatment is resumed. This possibility has been also observed in mCRPC where patients who have stopped first-line treatment in the absence of disease progression can newly respond to the resumption of DOC-based chemotherapy [14–17].

On the basis of these data, we tried to evaluate if intermittent chemotherapy can improve the QL of patients receiving DOC as first-line therapy for mCRPC by a Phase II randomized prospective study. Considering the uncertainties concerning the role of extramustine phosphate (EP) in combination with DOC at the time of the study design, the study was formally designed as a 2 × 2 factorial trial which also tried to test the role of EP addition to DOC. The present paper is specifically devoted to assess only the impact of intermittent chemotherapy on patients' QL compared with continuous treatment.

Patients & methods

• Patients

Patients with progressive mCRPC according to Prostate Cancer Working Group II criteria were considered eligible for the trial [18]. The exclusion criteria included previous chemotherapy (treatment with EP was not considered an exclusion criterion) or radiation, flutamide or any other oral hormones including steroids in the previous 4 weeks, or bicalutamide in the previous 6 weeks. No previous treatment with therapeutic radioisotopes was allowed.

A good performance status (ECOG 0–1) was required, as was adequate bone marrow, hepatic and renal function (absolute neutrophil count ≥1500/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥10 g/dl, serum bilirubin ≤1.5-times the upper normal limit (UNL), transaminases no more than twice the UNL and creatinine ≤1.5-times the UNL).

The other exclusion criteria were major cardiovascular diseases or comorbid conditions limiting survival, and an inability to complete the QL questionnaire. Patients with a previous malignancy other than nonmelanoma skin cancers had to have been disease free for 5 years.

All of the patients gave their written informed consent to participate in the study, which was approved by our local Ethics Committees and recorded in Italian Health Ministry trials registry (No. 2006-005728-17).

• Study design & procedures

The design of the present study reflected the results of a previous Phase II randomized trial conducted by our group, which demonstrated that a reduced DOC dose of 70 mg/m^2 without prednisone showed similar activity compared with the reference schedule of DOC 75 mg/m^2 with continuous prednisone 10 mg/day and that the addition of EP to chemotherapy led to better disease control [19].

From these results, we designed a randomized, 2 × 2 factorial Phase II trial, where the patients were randomly assigned to receive DOC 70 mg/m^2 administered as a 1-h intravenous infusion on day 1 (± thrice daily oral EP at a total daily dose of 840 mg on days 1–5) every 3 weeks for eight cycles or the same treatment with a 3-month interval after the first four courses.

Oral prednisolone (50 mg) was planned 12, 3 and 1 h before, and 12, 24 and 36 h after DOC administration. As reported before, we did not plan continuous administration of prednisolone 10 mg/day during chemotherapy because of the experience of our group in a previous trial [19].

• Study objectives & outcome assessment

The primary objective of the trial was to evaluate whether intermittent treatment (experimental arms C + D) had a different impact on the patients' QL from that of continuous treatment (standard arms A+B). To this end, the patients were asked to complete the EORTC QLQ-C30 questionnaire [20,21] before the first treatment administration, every two treatment courses, 1 month after the last chemotherapy, and (in the case of patients out of post-trial treatments due to progressive disease) 12 months after randomization: in the intermittent arms, an additional assessment was planned 1 month after the administration of the fourth course (at the beginning of the planned treatment interruption). Differences from baseline in general health status and the other QLQ-C30 scores were calculated at each time point. As stated before, the other comparison allowed by the 2 × 2 factorial design, DOC (A + C arms) versus DOC + EP (B + D arms), is not described in the present paper.

The secondary objectives were to assess biochemical responses, the incidence of pain and any changes in the incidence, the rates of

patients free of progression 9 months after randomization (corresponding to the ideal end of the intermittent treatment), progression-free survival (PFS) and overall survival (OS), and toxicity. Biochemical responses referred to the maximum change (increase or decrease) at any time during treatment. Pain was assessed using the short form of the Italian version of the Brief Pain Inventory (BPI) [22], which was administered together with the QLQ-C30 questionnaire. We also calculated the analgesic consumption score normalized to morphine equivalents at the time of each chemotherapy course [23].

Toxicities were graded using the National Cancer Institute common toxicity criteria (version 3.0).

• Statistical considerations

We used the effect size method to define the magnitude of the effects and chose a medium value of effect of 0.5 [24], which is generally considered clinically significant for any health-related QL end point [25].

By randomizing 64 patients in both intermittent and continuous arms, the study would have a power of 80% power with a (two-sided) type I error of 5%. Assuming that 15% of the patients would be unassessable, it was therefore planned to recruit a total of 148 patients.

The QL was assessed by analyzing the changes over time in the QLQ-C30 scores using the analysis of variance for repeated measures. All of the patients in the intermittent arms who at least entered the second treatment period, and all of the patients in the continuous arms who received at least five treatment courses were considered evaluable for testing QL differences.

Changes in the BPI scores over time were considered of clinical interest in the presence of a difference of two points on the 11-point numeric rating scales [26]: patients whose scores decreased by at least two points were considered to have 'improved,' and those whose scores increased by at least two scale points were considered to have 'worsened'.

Differences in the continuous variables were assessed using a paired t test, and differences in the categorical variables were assessed using Fisher's exact test. Kaplan–Meier analysis was used to assess survival duration.

In accordance with the suggestions of Tournigand *et al.*, who tested intermittent chemotherapy in patients with colorectal cancer [11], if the resumption of chemotherapy after the treatment interval did not lead to disease control in the case of biochemical progression alone during the interval, the time of progression was defined as the time the disease progressed during the interval itself.

The data were statistically analyzed using SPSS 12 (SPSS Inc., IL, USA) and Epi Info 2000 v 1.1.1 software (CDC, GA, USA).

Results

• Patient characteristics

The trial involved 148 centrally randomized patients: 75 patients were treated with continuous DOC and 73 with intermittent DOC. Four patients were never treated because they withdrew their informed consent (n = 2) or died for reasons unrelated to mCRPC before treatment was started (n = 2). The main characteristics of the randomized patients are shown in **Table 1**.

• Treatment administration & supportive therapies

The patients enrolled in the continuous arms received the full treatment less frequently (57.5%) than those enrolled in the intermittent arms [73.2%], mainly because of early treatment interruptions due to the more frequent side effects in the continuous arms (19.2 vs 5.6%) **(Table 2)**. The percentage of patients treated with granulocyte colony-stimulating factors was similar in the continuous and intermittent arms. Bisphosphonate therapy was administered to 41 patients (20 in the continuous arms and 21 in the intermittent arms), all but one of whom was continuing previously prescribed biphosphonates or had started the treatment at the time of entering the study.

• Outcomes

QL outcomes

Assessable QL data were available for 111 patients (55 in the continuous and 56 in the intermittent arms); the remaining patients were excluded from the analysis because of early study withdrawal or because the questionnaire was not administered at baseline and/or at one or more of the subsequent time points (thus making it impossible to detect differences between the two treatment modalities). In total, 15 of the 71 patients randomized to intermittent treatment withdrew from the study early because of progression [7], toxicity [4], the development of a concomitant pathology [1], death unrelated to progression [1] or before starting treatment [2].

Table 1. Patient characteristics.

Patients characteristics	Continuous docetaxel	Intermittent docetaxel
Pandomized patients (n)	75	73
Age:		
– Median (years)	68.5	70
Range (years)	47–80	48–81
Gleason score, n (%):		
– ≤7	28 (37.3%)	25 (34.2%)
– 8–10	44 (58.7%)	41 (56.2%)
– Unknown	3 (4.0%)	7 (9.6%)
Hormonal manipulations, n (%):		
– 2	52 (69.3%)	49 (67.1%)
– >2	23 (30.7%)	24 (32.9%)
Baseline serum PSA (ng/ml):		
– Median	51	56
– Range	1–3020	2–4212
Type of metastases, n (%):		
– Bone	67 (89.3%)	58 (79.4%)
– Nodal	30 (40.0%)	33 (45.2%)
– Visceral	12 (16.0%)	9 (12.3%)

PSA: Prostate-specific antigen.

Consequently, 56 were eligible to start the second DOC series after the treatment-free interval. **Figure 1** shows the trend of prostate-specific antigen (PSA) levels during the interval and the resumption of chemotherapy.

There was no statistically significant difference in general health status between the continuous and intermittent arms at any of the assessments, and the same was true of the other QLQ-C30 scales **(Figure 2)**. The results were not different by adjusting for EP addition (data not shown).

Table 2. Treatment (patients receiving at least one docetaxel course).

	Continuous docetaxel, n (%)	Intermittent docetaxel, n (%)
Treated patients (n)	73	71
Number of cycles:		
– Total	439	482
– Median (range)	8 (2–8)	8 (1–8)
Delayed infusions (%)	5.7	5.2
GCSF use	5 (6.8)	4 (5.6)
Concurrent disphosphonate administration	20 (27.4)	21 (29.6)
Reasons for stopping treatment:		
– Protocol completed	42 (57.5)	52 (73.2)
– Disease progression	13 (17.8)	13 (18.3)
– Toxicity	14 (19.2)	4 (5.6)
– Withdrawal of consent	2 (2.7)	
– New concomitant disease	2 (2.7)	1 (1.4)
– Death unrelated to disease or treatment		1 (1.4)
Subsequent chemotherapy	34 (46.5)	41 (57.7)
DOC rechallenge	28 (38.7)	27 (38.4)

GCSF: Granulocyte colony-stimulating factor.

Other outcomes

Forty-three of the 114 patients evaluable for QL declared that they experienced pain at baseline. During treatment, 22 showed a 2-point improvement in their BPI score (13 and nine in the continuous and intermittent arms, respectively), and nine a 2-point worsening (four and five in the continuous and intermittent arms, respectively). There were no differences in the changes in the analgesic scores between the treatment groups.

At least a 50% decrease in PSA levels was observed in 66.2% of the patients in the continuous arms and 60% of those in the intermittent treatment arms **(Table 3)**.

Nine months after randomization, 15.9 and 43.2% of the patients treated with continuous and intermittent DOC were progression free, respectively (χ^2 test = 12.65; p = 0.0003), and the projected 9-month PFS rates were, respectively, 15.2 and 34.3% (log-rank test: p = 0.01).

After a median follow-up of 21 months (range: 1–62), 37 patients are still alive. The median survival of the patients treated in the continuous and intermittent arms was respectively 21 and 24 months, and the 2-year OS rate was, respectively, 40.9 and 47.1%. After the study, 75 patients received further chemotherapy (56 a DOC rechallenge).

Table 4 shows the hematological toxicities, which were generally mild–moderate and short lasting, and resolved without the need for treatment discontinuation. Two patient developed grade 3–4 anemia, but none grade 3–4 thrombocytopenia. Grade 3–4 hematological toxicities were reported more frequently in the continuous arms than in the intermittent arms (17.8 vs 7%).

Discussion

This study, which is the first to test a truly intermittent approach to the first-line chemotherapy of mCRPC in an attempt to improve patient compliance and reduce the burden of treatment, failed to demonstrate any QL advantage in comparison with continuous treatment.

In the oncological world, the term 'intermittent chemotherapy' has often been used to indicate two different strategies: in one, patients stop the treatment after having completed a predefined number of chemotherapy courses without disease progression, but may subsequently

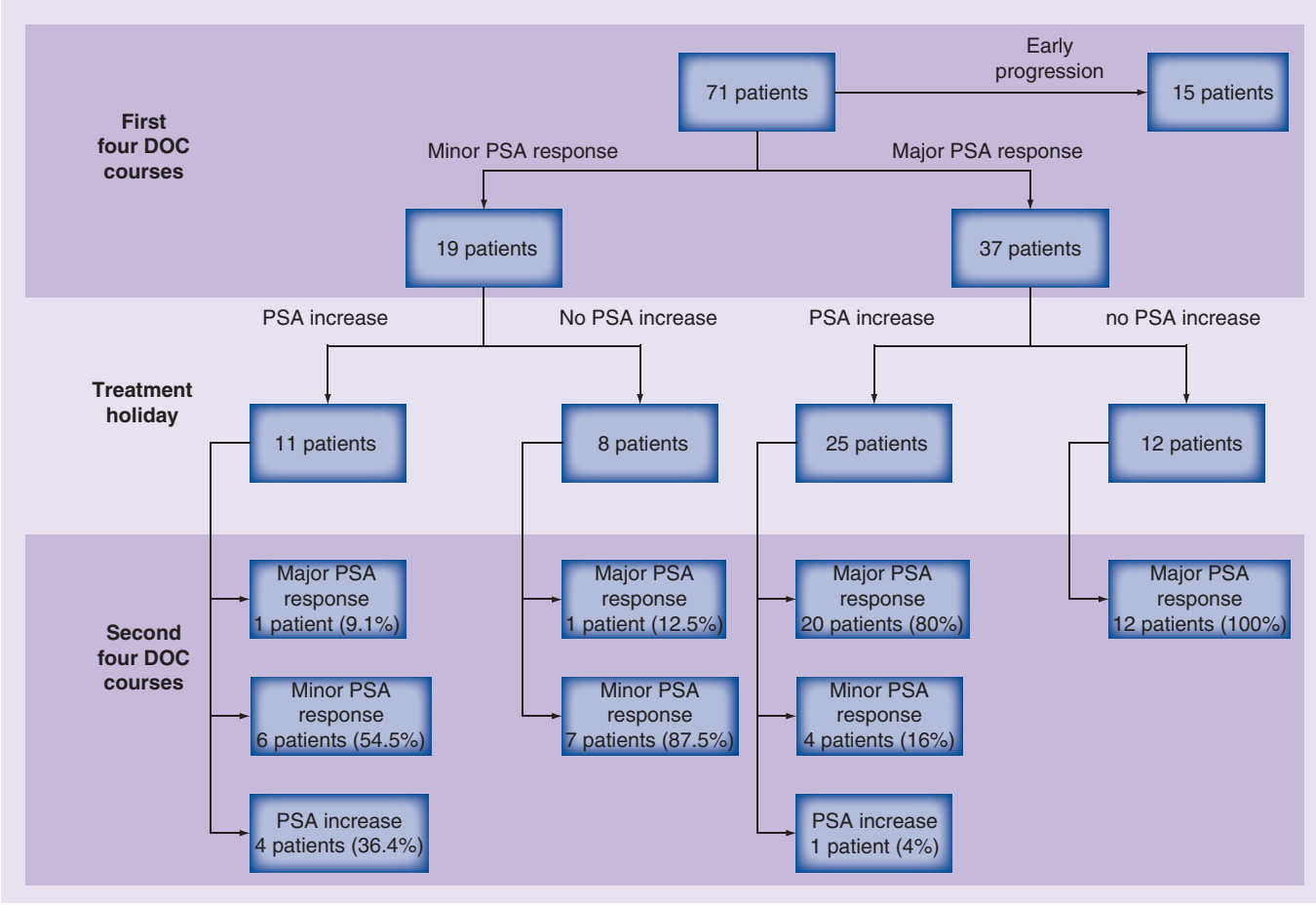

Figure 1. Biochemical outcomes during intermittent treatment.
DOC: Docetaxel; PSA: Prostate-specific antigen.

resume it at any time the tumor progresses; in the other, patients stop the treatment after having received a limited and defined number of cycles, and then resume it after a pre-established interval. The time of the resumption of treatment is therefore different: in the first case, it is established by the progression of the disease and it would be more appropriate to refer to it as a rechallenge (or retreatment); in the second, it is predefined and does not depend on disease progression, and the strategy can be considered truly intermittent.

In the case of prostate cancer, the concept of treatment intermittence has been developed in the setting of hormone-sensitive advanced disease. Patients with hormone-sensitive disease undergo androgen deprivation for extended periods of time, which leads to a number of side effects capable of impairing their QL: consequently, there has been an increasing tendency to adopt intermittent androgen deprivation by suspending the treatment after a prolonged period of PSA normalization and resuming it at the time of biochemical progression. However, a recent Phase III trial failed to demonstrate the noninferiority of this approach in comparison with continuous androgen deprivation [27].

In the field of mCRPC, the idea of intermittence has generally been associated with a rechallenge, particularly in the absence of second-line therapies. Various studies have shown that patients who stop first-line DOC without progressing remain sensitive to the drug and that prolonged disease control can be obtained by reintroducing it once or more times when progression occurs [14–17,28].

The aim of this strategy is clearly to exploit the potential activity of chemotherapy after it has been suspended not because of the onset of resistance (disease progression) but because of the completion of the planned number of courses, which is usually determined on the basis of median cumulative toxicity and is strictly linked to the concept of the sensitivity/

resistance of a specific tumor to a specific drug. This approach is different from that used in our study insofar as the treatment was divided into two periods of four DOC courses separated by a preplanned interval of 3 months with the aim of reducing toxicity and improving patient compliance.

The implications and end points of a trial designed to test intermittent chemotherapy in mCRPC patients were extensively reviewed by Lin *et al.* [29]. The first and most obvious implication is disease control as reflected by PFS: the off-therapy period could lead to rapid disease progression, which may not be halted by resuming treatment. In our experience, intermittent chemotherapy was not detrimental in terms of disease control as the survival rates were similar in the intermittent and continuous arms. Furthermore, as observed in rechallenge experiences, our results confirmed that the large majority of patients who have achieved good biochemical disease control during the first DOC series retain this response despite the increase in PSA levels during the treatment interval. Similarly, the probability of achieving biochemical disease control during the second DOC series was very low in the patients who did not show a good PSA response during the first treatment period.

Another important issue is how to define the concept of PFS, which should be done cautiously in the case of a trial of intermittent chemotherapy: PFS is usually calculated from the start of chemotherapy to the date of disease progression, but how should progression be considered during the off-therapy period? One possible answer to this question is that proposed by Tournigand *et al.*, who identified the time of progression as falling during the off-therapy period whenever the resumption of treatment was unable to restore disease control [11]. Using this definition of PFS, we found that

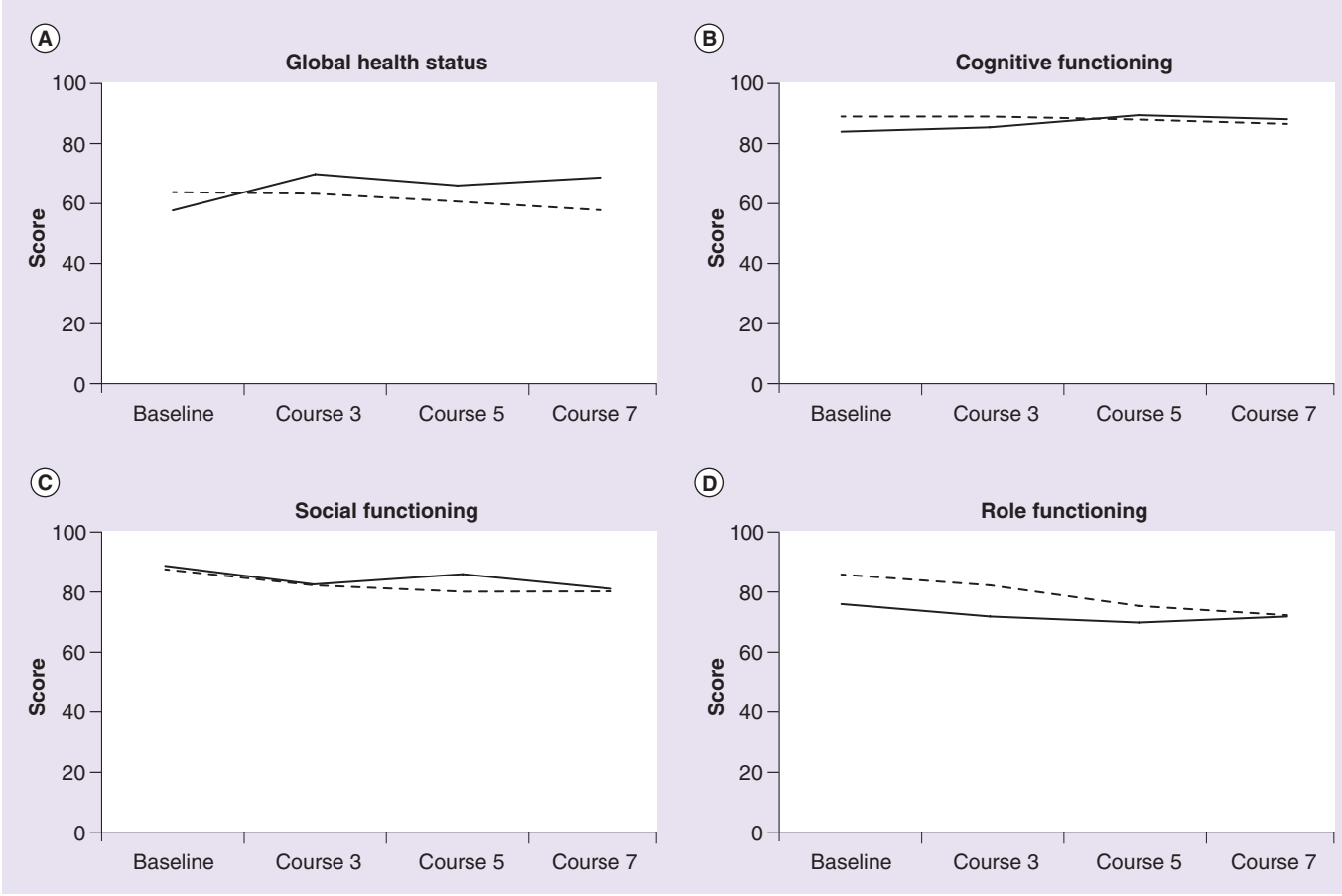

Figure 2. General health status and selected quality of life outcomes. The figures report the changes in the scores of the quality of life subscales at the different assessment time points. **(A)** General health status; **(B)** cognitive functioning; **(C)** social functioning; and **(D)** role functioning.

intermittent therapy led to a 1-month advantage which, although statistically significant, may be of only marginal clinical relevance: in any case, it did not change OS.

QL issues should have a central place when considering intermittent therapy for mCRPC: unlike in the case of other cancers for which chemotherapy is usually administered until progression, the pivotal DOC studies of mCRPC were based on a defined duration of therapy, and it is now widely accepted that treatment should be stopped after 8–10 DOC courses even in the absence of progressive disease [1,2]. An intermittent strategy should therefore mainly target a QL improvement in order to reduce the burden of the side effects due to continuous treatment.

Our experience failed to support the hypothesis that a treatment holiday would allow patients to recover from side effects and improve their QL. There was no difference in any of the QL domains between the patients treated intermittently or continuously. However, it is worth noting that the rate of toxicity-related study withdrawals was twice as high in the continuous arms, suggesting a worse compliance to continuous treatment.

Our study has at least two limitations. First of all, we chose a reduced dose of DOC, which was administered without the continuous administration of prednisone. In the pivotal trials, DOC was administered at a higher dose, while prednisone was mainly required by the need to have the same drug administered with chemotherapy in both the reference and experimental arms. This may have beneficial effects in terms of both disease control and QL, but it can also lead to side effects, which may become increasingly clinically relevant in the light of the need to administer long-term concomitant steroidal treatment not only in first-line therapy but also in second-line treatment with cabazitaxel or abiraterone [30]. Our choices in the present trial reflected the previous experience of our group, where DOC dose reduction and prednisone lack did not reduce the activity of DOC [19] compared with other experiences [31]. Moreover, it is noteworthy that since all treatment groups received the same DOC dose without prednisone, this therapeutic strategy did not affect the results in terms of QL comparison between intermittent and continuous treatment, but only may limit the comparability with other studies on mCRPC patients.

Another question may arise from the choice of treatment holiday, since the decision to use four DOC courses before the treatment interval was arbitrary, as was the choice of the duration of the interval itself.

Table 3. Clinical outcomes.

	Continuous docetaxel	Intermittent docetaxel	p-value
9-month disease control rate	15.9%	43.2%	0.0003
9-month PFS	15.2%	34.3%	0.01
PSA ↓50%	60%	66.2%	NS
Median survival	21 months	24 months	NS
2-year overall survival	40.9%	47.1%	NS

PFS: Progression-free survival; PSA: Prostate-specific antigen; NS: Not significant.

Conclusion

The maintenance of QL of patients with mCRPC should be a primary objective for the oncologists together the survival increase. Although DOC-based treatments seem to improve (or at least to maintain) the patients' QL, some patients may experience the cumulative burden of side effects during treatment, mainly when they are old or present several comorbidities. Intermittent chemotherapy was considered as a mean to improve patients' compliance, but in our experience, which is the first which explored this possibility, although the intermittent strategy proved to be feasible and had no detrimental impact on disease control, it had no advantage in terms of the QL and should therefore no longer be considered for patients with mCRPC.

Future perspective

After DOC became the reference first-line treatment, it is only recently that new agents have been demonstrated to be active in mCRPC patients who have received first-line DOC, by significantly prolonging their survival. These agents show significant differences in toxicity

Table 4. Patients experiencing grade 3–4 toxicity.

Toxicity	Continuous docetaxel, n (%)	Intermittent docetaxel, n (%)
Anemia	2 (2.7)	
Neutropenia	13 (17.8)	5 (7.0)
Anorexia	1 (1.4)	
Allergy	1 (1.4)	1 (1.4)
Diarrhea		1 (1.4)
Nausea		1 (1.4)
Fatigue	3 (4.2)	
Fever		1 (1.4)
Infection	1 (1.4)	
Febrile neutropenia	3 (4.1)	3 (4.2)
Deep vein thrombosis	2 (2.7)	3 (4.2)

profile, with common feelings that hormonal agents (abiraterone acetate and enzalutamide) and radiopharmaceuticals (radium-223) are better tolerated than chemotherapeutics agents (DOC or cabazitaxel). However, when one of these agents is adopted all of the patients eventually became resistant to the therapy and require further treatments. So, without a clear superiority of one of these agents over the others, the future challenge in decision-making process will be to choose the right drug for the right patient in the aim of preserving patients' QL. Intermittent chemotherapy was considered as a mean to reduce the impact of chemotherapy on the patients' QL but this approach failed to achieve this goal in mCRPC. Due to the impressive improvements in survival of mCRPC patients leading to an increasing rate of long-term survivors, more efforts should be made to identify the best strategy able to maintain (or improve) patients' QL in the whole and over the time. In this view, further prospective studies could investigate different durations of chemotherapy breaks or the real needs of adding prednisone to chemotherapeutic agents.

Financial & competing interests disclosure

U Basso received honoraria from Sanofi Aventis. O Caffo received honoraria from Sanofi Aventis and Janssen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investi-gations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

- Eight to ten docetaxel (DOC) courses represent the standard first-line treatment for metastatic castration-resistant prostate cancer (mCRPC) patients.
- Although DOC-based treatments have improved (or at least have not worsened) the patients' quality of life (QL), there is a common feeling in everyday clinical practice that some patients may experience the cumulative burden of side effects during treatment.
- One possible means of improving the patients' QL is to administer intermittent rather than continuous chemotherapy, as has been tested in patients with metastatic breast cancer and metastatic colorectal cancer.
- We tried to evaluate if intermittent chemotherapy, administered with a 3-month fixed treatment holiday, can improve the QL of patients receiving DOC as first-line therapy for mCRPC by a Phase II randomized prospective study.
- We failed to demonstrate any QL advantage in comparison with continuous treatment.
- The intermittent strategy proved to be feasible and had no detrimental impact on disease control.
- Intermittent chemotherapy should therefore no longer be considered for patients with mCRPC.

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