INTRODUCTION

Recently, data from two large phase III clinical trials, TAX327 and SWOG 9916, showed a survival benefit for treatment with docetaxel-containing chemotherapy compared to mitoxantrone-based therapy in patients with androgen-independent prostate cancer. The median overall survival rates for patients in the TAX327 trial [1] treated with docetaxel every 3 weeks was 18.9 months, compared with 16.4 months for those in the control arm (P = 0.009). Patients treated with the combination of docetaxel and estramustine in the SWOG 9916 [2] trial also had a significant improvement in median survival (18 vs 16 months, P = 0.01), a longer progression-free survival (6 vs 3 months, P < 0.001), and a 20% reduction in the risk of death. While the results of these two randomized studies established docetaxel-based chemotherapy as the standard-of-care for first-line treatment, the optimum treatment duration remains to be established, particularly in responders. A maximum of 12 cycles was given in the SWOG trial, and the treatment duration in all three arms of the TAX327 trial was 30 weeks, a period arbitrarily selected. However, currently it is widespread practice to treat patients indefinitely until there is unacceptable toxicity or disease progression. This exposes responding patients to uninterrupted chemotherapy for prolonged periods, with the consequent increased risk of toxicity. Thus the potential benefit obtained with chemotherapy might be hampered by the threat of long-term toxicity. Long-term adverse effects associated with continuous docetaxel treatment include asthenia, oedema, peripheral neuropathy and cytopenia.

Intermittent administration of chemotherapy for the treatment of prostate cancer, with systematic ‘drug holidays’ for patients who have a response, is an attractive approach. In this way the development of progressive treatment-related toxicity might be reduced or delayed, with comparable disease control and improved quality of life (QoL). Whether intermittent chemotherapy can be beneficial for some patients with prostate cancer is as yet unanswered.

The issue of intermittent vs continuous therapy has been addressed in five phase III trials in other oncological diseases like metastatic breast [3–6] and colorectal cancer [7]. Regardless of the differences in study design and considering the limitations of each study, there appears to be no significant difference in overall survival between intermittent and continuous chemotherapy in these two diseases. Time to progression favored continuous treatment, but this factor was variably defined. If time to progression was defined as the interval from the date of randomization to disease progression during or after completing re-induction chemotherapy (i.e. time to chemotherapy resistance), there was no statistically significant difference between the continuous and intermittent arms. Response rates on re-introducing the same chemotherapy after a ‘drug holiday’ period were only evaluated in two of these studies. In these trials, all and 47% of patients, respectively, achieved at least stable disease, providing evidence that the disease might be responsive on re-treatment in chemotherapy-sensitive patients. However, formal QoL assessments were inconsistently evaluated and consequently, definitive conclusions as to a potential benefit on QoL of intermittent therapy cannot be made.

In prostate cancer there is limited information on whether continuous therapy offers an advantage over intermittent therapy, in terms of disease control, overall survival, treatment-related toxicities and QoL. There are no randomized phase III trials comparing intermittent with continuous chemotherapy in metastatic hormone-refractory prostate cancer, but data from three single-arm trials using intermittent weekly docetaxel-based chemotherapy are available.

Beer et al. [8,9] prospectively tested intermittent chemotherapy in eight patients with androgen-independent prostate cancer who responded to calcitriol plus docetaxel [10] (22% of the 37 patients who were initially treated with this regimen) based on serum PSA response by consensus criteria [11]. Chemotherapy was resumed after an increase in PSA level by half and of ≥1 ng/mL. The duration of chemotherapy ‘holidays’ was clinically meaningful, with the median (range) duration of the first treatment ‘holiday’ being 20 (13–74) weeks, and all patients retaining sensitivity to re-treatment. Four patients were eligible for a second chemotherapy ‘holiday’, which lasted a median of 21 (17–28) weeks. Furthermore, two patients elected to take a third chemotherapy holiday, which lasted 10 and 28 weeks, respectively. The median (95% CI) time to treatment failure was 26.3 (23.6–29.4) months, and the median survival was 41 (33.7–48.3) months. Although limited by the small sample size and the lack of a control arm, QoL (using the QLQ-C30 questionnaire) measures (with each patient used as his internal control) showed a significant improvement in fatigue, but there were no
differences in any of the function scales of QLQ-C30.

The ASCENT [12,13], a multi-institution randomized phase II clinical trial, was designed to compare the activity and safety of weekly calcitriol (45 μg on day 1) plus docetaxel (36 mg/m² i.v. on day 2 for 3 weeks of a 4-week cycle) to placebo plus docetaxel in patients with chemotherapy-naïve metastatic hormone-refractory prostate cancer. In that study, intermittent chemotherapy was prospectively evaluated in those patients who chose to interrupt treatment if they had a confirmed ≥ 50% reduction in serum PSA level and a serum PSA level of ≤4 ng/mL. PSA was monitored every 4 weeks (with CT every 8 weeks in patients with measurable disease) during the treatment 'holiday'. Treatment was resumed when the serum PSA level increased by half or more and was ≥2 ng/mL, or for other evidence of disease progression. The study was not powered to compare the outcomes of a treatment holiday between the arms. Of the 250 patients enrolled, 18% (calcitriol 20%, placebo 16%) received intermittent chemotherapy. The median duration of the first chemotheraphy holiday was 4 (4–74+) months (calcitriol 15 weeks, placebo 16 weeks). Interestingly, on resuming treatment after the first 'holiday', half the patients responded with a reduction in serum PSA level of half or more from their baseline after the ‘holiday’.

Based on a different approach, the third trial was a single-arm, phase II study reported by Miller et al. [14]; in that study, 75 patients with hormone-refractory prostate cancer and biochemical (PSA) or clinical progression received weekly docetaxel 35 mg/m² with estramustine (140 mg orally, three times daily on days 1–3, 8–10, and 15–17). The design of the study differed from the two previously described strategies, in that treatment was interrupted after three cycles if there was no progressive disease. Treatment was restarted when the PSA levels doubled (compared with the nadir) or if progression was suspected for other reasons. The primary endpoint was best response (clinical and/or PSA) to first subsequent re-treatment (sequence 2) with a PSA response defined as a reduction by half or more in the PSA level from baseline, lasting ≥4 weeks. There was a PSA response in 76 (67–84%), 80 (67–90%), 57 (38–74%) and 29 (5–66%) of patients for courses 1, 2, 3 and 4, respectively. The median chemotherapy-free intervals were 2.8, 2.8 and 2.5 months after course 1, 2 and 3, respectively. With a median follow-up of 9.1 months, the median overall survival was 18.9 months.

Collectively, findings in these single-arm trials show the feasibility of intermittent chemotherapy in androgen-independent prostate cancer. However, conclusions on the benefit of this approach are limited by the sample size and the use of non-standard chemotherapy regimens of these non-comparative studies.

The use of less toxic, biological agents during the drug ‘holiday’ could also be a potential strategy that might prolong the time off chemotherapy, and therefore the time to tumour re-growth. It was hypothesized that, after the cytotoxic action of chemotherapy, there might be an increased tumour cell proliferation rate due to improved access to nutrients and the action of growth factors. This might result in an induced resistance to the chemotherapy. Therefore, it seems plausible, as suggested by Lin et al. [15], that the use of other than chemotherapeutically active agents between chemotherapy cycles might prevent tumour re-growth after chemotherapy-induced cell death. Notably, none of the studies addressed the role of maintenance biological therapy during the periods off chemotherapy. Potentially, this approach might allow the oncologist to continue treating the disease for prolonged periods, with improved benefit and less toxicity.

Future phase III studies testing intermittent vs continuous chemotherapy incorporating overall survival, time to chemotherapy resistance, QoL and cost–utility endpoints are needed to determine more definitely the potential benefits of this approach. Furthermore, the possible contribution of adding biological maintenance therapy should also be addressed.

CONFLICT OF INTEREST

None declared.

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COMMENTS

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Abbreviation: QoL, quality of life.