Whole Blood Stem Cell Reinfusion and Escalated Dose Melphalan in Castration-Resistant Prostate Cancer: A Phase 1 Study

Jonathan Shamash1, Jimmy Jacob2, Samir Agrawal1, Thomas Powles1, Katherine Mutsvangwa1, Peter Wilson1, and Justin Stebbing1

Abstract

**Purpose:** Nontaxane-based chemotherapeutic options in castrate-resistant prostate cancer (CRPC) are limited despite the long natural history of the disease. We carried out a phase 1 dose-escalation study of the alkylating agent melphalan with autologous stem cell transplantation, comparing rapid changes in circulating tumor cells (CTC) and prostate-specific antigen (PSA) as a measure of response.

**Experimental Design:** Cohorts of individuals with advanced CRPC received high-dose intravenous melphalan, and autologous blood was returned to patients during treatment. The efficacy endpoints were the PSA reduction rate, CTC response, survival parameters, toxicity and whether reinduction of endocrine sensitivity occurred.

**Results:** Twenty-four patients were recruited. Dose escalation was feasible with the highest dose cohort being reached. Of 23 individuals evaluable for response, 16 had a PSA response of more than 30%; of 11 patients with soft tissue disease, 4 achieved a partial response and 7 had stable disease. Patients with CTC counts that decreased to less than 5 within 2 weeks from the start of therapy had a longer overall survival (30.6 months vs. 15.3 months, \( P = 0.03 \)). Treatment was associated with myelosuppression and frequent hospitalizations. In 20 patients after the study, hormone therapy was reintroduced when PSA increased again; response rates were high.

**Conclusions:** Autologous transplantation following high-dose alkylating agent chemotherapy induces responses but proved toxic, although dose escalation proved possible. The possibility of using CTCs to identify responders at two weeks may be used to justify such an intensive approach. Many individuals went on to further respond to both docetaxel and hormonal therapy. *Clin Cancer Res; 18(8); 2352–9. ©2012 AACR.*
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individuals who are likely to have a prolonged survival
Because we have previously shown that we can identify
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stem cells were mobilized on each cycle using a short 4- to 5-
given every 2 weeks in the setting of CRPC. The dose of
in whole blood could support multiple cycles of melphalan
(15–17). We therefore investigated this approach in a dose finding
study to observe whether lenograstim mobilized stem cells
in whole blood could support multiple cycles of melphalan
given every 2 weeks in the setting of CRPC. The dose of
melphalan was escalated and unlike previous studies the stem cells were mobilized on each cycle using a short 4- to 5-
day course of high-dose lenograstim before venesection. This
allowed fixed timing of venesection and administration of melphalan. To understand the effects of this therapy, as well as measuring prostate-specific antigen (PSA), we also
analyzed levels of circulating tumor cells (CTC) before and during therapy (18) following convincing data for their utility in this setting including superior correlations with outcome compared with PSA measurements (19, 20).
Because we have previously shown that we can identify
dividuals who are likely to have a prolonged survival
within 1 month of commencing a new therapy (21), we
wished to see whether such an approach could be used here.

**Patients and Methods**

The study aim was to determine the safety and efficacy of intensified intravenous melphalan with whole blood stem cell transplantation in patients with CRPC. The primary endpoint was to determine the dose-limiting toxicity of the schedule. The efficacy endpoints were the PSA reduction rate, CTC response, and whether reininduction of endocrine sensitivity occurred. Quality of life (QoL) was assessed before treatment and at 2-weekly intervals for 8 weeks and then 1 month after the completion of chemotherapy. Computed tomography and isotope bone scanning was carried out 12 weeks after the start of therapy. The EORTC QLQ-C30 quality of life questionnaire together with prostate-specific module QLQ-PR25 was used to measure 5 functional scales (physical, role, emotional cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), a global health status/QoL scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The study was approved by the Local Ethics Committee.

All patients recruited had biopsy proven CRPC and evidence of tumor progression using the PCWG2 criteria (22); all were symptomatic and prior chemotherapy was not permitted. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2, an unsupported hemoglobin of more than 110 g/L, no contraindication to large volume venesection (e.g., active angina or heart failure) and a life expectancy of at least 12 weeks. Patients had pretreatment investigations consisting of computed tomography of the chest, abdomen and pelvis, a bone scan, full laboratory investigations including lactate dehydrogenase (LDH) and in addition blood was drawn for CTCs as we have described (23, 24). Lenograstim was administered at a dose of 10 mcg/kg for 3 days. Initially patients went on to have chemotherapy regardless of the prechemotherapy CD34 count on the 4th day, but after 2 patients failed to mobilize and were found to have low CD34 counts the protocol was modified such that patients who failed to have a CD34 count of more than 9 microliters after 3 days of lenograstim were withdrawn from the study. Patients were recruited in cohorts of 3 and 6 dose levels were planned. The volume of blood venesected was dependent on patient’s weight. Those patients weighing more than 80 kg had 1,000 mL venesected and those weighing less had 750 mL venesected. The blood was collected in a Baxter blood donation bag with anticoagulant and refrigerated at 4°C. Intravenous melphalan was given over 15 minutes and patient’s had their autologous blood returned the following day at least 12 hours after the melphalan (day 0). On day 9, lenograstim was restarted this time for 5 days. On day 15 (2 weeks after the previous cycle), if the complete blood count showed a neutrophil count of greater than 1 regardless of CD34 count, blood was venesected and the melphalan given. A total of 4 cycles given over 42 days was planned.

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**Translational Relevance**

The treatment of prostate cancer is changing with the realization that castrate-resistant prostate cancer (CRPC) can still respond to different forms of androgen deprivation. Traditional chemotherapeutic approaches however still remain the mainstay of therapy for CRPC and herein, we present a new study, the first of its kind, examining the role of stem cell transplantation in heavily pretreated CRPC. Melphalan, an alkylating agent, was used in escalating doses with significant G-CSF support. Although the therapy was toxic, use of circulating tumor cells (CTC) and not prostate-specific antigen, was able to rapidly predict those who would benefit. In those with decreasing CTCs within a month, survival was prolonged, and we therefore present a new possibility for those with resistant disease. This has never been attempted before and strengthens the role of CTCs in this setting.

Working in up to 40% of cases when patients were rechallenged following failure of chemotherapy (13). Here, we hypothesized that more intensive chemotherapy would increase the number of patients achieving disease control and allow a greater number to benefit from this effect.

To study the effects of alkylating agents further, we have used melphalan as an option because it is not only suitable for dose intensification but also its short half-life means that it is suitable for hematologic support using unprocessed autologous whole blood from patients given high-dose lenograstim to increase the number of CD34-positive progenitor cells. This has been shown in myeloma, however in these cases, the process has generally only been used to support a single high-dose treatment and not multiple cycles (14). In the management of small cell lung cancer and ovarian carcinoma, such a process has also been used to support multiple cycles of carboplatin-based chemotherapy (15–17).

"Patients and Methods"

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Laboratory tests including CTCs were taken before each cycle of melphalan. Prophylactic ciprofloxacin, was given from days 5 to 15; following a case of proven fungal infection itraconazole suspension 200 mg 2×/d was added to the prophylactic regimen and given continuously. In addition, all blood products were irradiated. A schematic of the protocol is shown in Fig. 1. Dose-limiting toxicity and cohort expansion was assumed to have been found if either grade 3 or 4 mucositis occurred or if more than 1 patient required a delay in treatment of more than 1 week. If a patient failed to mobilize stem cells then an additional patient was recruited to the cohort.

Intercooled Stata 8.2 for windows was used for the statistical analysis. The Wilcoxon matched-pairs signed-rank test was used to assess the median differences between baseline QLQ-C30 scores and scores at the start of subsequent cycles. To test the equality of survivor functions between groups the log-rank test was used.

Results

Between January 2007 and January 2011, 24 individuals were recruited and received melphalan according to the schedule outlined. The patient characteristics are shown in Table 1; all had received maximum androgen blockade, nearly half had received corticosteroids and/or estrogens. Seventeen (71%) had increased alkaline phosphatase and 10 had a increased LDH before therapy. The doses of each cohort are shown in Table 2. Cohort 4 was expanded following the failure of 2 patients to mobilize CD34 cells in response to the initial lenograstim. Those patients are included in the analysis.

PSA response

The maximal PSA response to melphalan alone is shown in a waterfall plot (Fig. 2). Overall 16 (67%) had a decrease in PSA, and the nadir was reached at a median of 7 weeks (range 4–21 weeks) following the start of melphalan. Nine (38%) had at least a 30% reduction in PSA by 12 weeks. The median time for the PSA to reach its nadir was 54 days (range 3–152 days). The median time to progression based on PSA alone measured 2.8 months (95% CI: 2.0–3.7) on melphalan.

Radiologic response

Bone scans and computed tomography were repeated at 12 weeks, and 23 patients were assessable for bone scan response. Four patients (17%) showed progressive disease using the PCWG2 criteria. In 1 patient this occurred despite a decrease in CTC counts and relief of bone pain (this may have represented a pseudoprogression but he was lost to follow-up before a further scan could be arranged). Eleven patients were assessable for their soft tissue disease and of...
these 4 (36%) achieved a partial response and 7 (64%) had stable disease.

CTCs

CTCs were measured in 16 patients. In 10, there were 5/7.5 mL or more. In 9, they decreased to less than 5 within 6 weeks. Patients with increased CTCs had a numerical nonsignificant shorter progression-free survival (5.7 vs. 9.2 months, P = 0.19) although median overall survival was similar (27 vs. 30.6 months). Those patients who had increased numbers of CTCs at the start of therapy showed a rapid response. In 4 patients, the CTC count decreased to less than 5 after 1 cycle of melphalan (2 weeks after start of chemotherapy). These patients had a prolonged overall survival (30.6 months vs. 15.3 months, P = 0.034). At 4 weeks, there was an association between CTC levels and PSA change. Those patients with increased CTC counts that had decreased to less than 5/7.5 mL (6 out of 10) had a median 36% decrease in PSA (range 17% increase to 65% decrease); those whose CTCs failed to come down to this level had a median 34% increase in PSA (range 4% increase to 221%, P = 0.033; Fig. 3). CTCs therefore were able to identify responding patients within 4 weeks of starting therapy, unlike PSA where changes showed greater variability.

Toxicity

Treatment was associated with significant toxicities (Table 3). There was 1 treatment-related death (cohort 2), and the patient had received all 4 cycles of melphalan. On the third cycle, he had significant neutropenic fever which resolved with neutrophil recovery. After the 4th cycle however, he became neutropenic and developed interstitial lung shadowing with respiratory failure. Postmortem examination confirmed the presence of invasive pulmonary aspergillosis despite appropriate antifungals; subsequent patients thus received itraconazole prophylaxis.

All patients developed grade 4 neutropenia with each cycle although this was short lived. However, 43% of cycles required hospital admission. Mucositis was not a serious problem, and there was no grade 3 or 4 diarrhea. Nearly all patients received the cycles within 24 hours of anticipated date. Following the 4th cycle, platelet recovery was delayed in 5 patients. The number of CD34 cells per microliter decreased with each cycle of treatment (cycle 1, 21; cycle 2, 15; cycle 3, 5; and cycle 4, 1)—but there was no correlation between the number of CD34 cells on cycles 2 to 4 and the subsequent duration of myelosupression. A median of 1 platelet transfusion per cycle was needed for the first 3 cycles and 3 following the 4th cycle.

Seven patients failed to complete the protocol. In 2 patients, this was because of failure to release stem cells following the initial lenograstim; both these patients received only 1 cycle of melphalan. In 1 patient, there was prolonged neutropenia after 2 cycles, one stopped after 3 cycles following a florid drug reaction to ceftriaxime (he was known to be penicillin sensitive). One patient had clear progression after 3 cycles, one stopped after persistent rapid atrial fibrillation while neutropenic, one stopped after significant septicemia on cycle 3. In all but the first 3, the blood count recovered to allow a 4th cycle had it been appropriate.
Rechallenge with previously failing endocrine agents

Hormone therapy was stopped during chemotherapy based on the theory that more cancer cells would be susceptible to chemotherapy. In addition, reintroduction of endocrine treatment often produces further responses. Following a subsequent PSA increase, the hormones that had failed were reintroduced in 20 patients: maximal androgen blockade in all and dexamethasone with or without diethylstilbestrol in those who had been exposed to these before melphalan. Overall 7 responded with a 50% or more reduction in PSA. Dexamethasone was restarted in 9 patients and 4 responses occurred. Diethylstilbestrol was given to 6 patients before melphalan of whom 3 responded when rechallenged. Overall 48% had a response to a hormone therapy that had failed before melphalan.

The time to failure for these re-introduced treatments measured 5.7 months (95% CI: 4.2–1.0). Overall 48% responded to rechallenge with prior hormone therapy. The median overall survival for all patients in the study was 27 months (95% CI: 16.2–not reached; interquartile range, 17.6–32.6 months).

QoL and pain response

At the start of the study, 80% of patients had pain due to their prostate cancer. There was a significant improvement in patients’ pain scores within 2 weeks of the start of chemotherapy (P = 0.001) which was maintained throughout the study (see Table 4) Fatigue and dyspnea increased after 2 cycles (4 weeks) compared with baseline (P = 0.009 and 0.004, respectively). These symptomatic scores correlated strongly with QoL globular scores.

Further therapy

Diethylstilbestrol was given to 6 patients who had not received it before melphalan, 4 responded for between 4 and 8 months. Sixteen went on to receive docetaxel without unexpected myelosupression. The median number of cycles given was 6 (range 2–6) with a 30% PSA response rate of 13% and a median time to progression of 4.1 months (range 1.0–8.4 months) showing that prior melphalan did not preclude standard subsequent treatment with this agent.

Discussion

As the treatment of CRPC is evolving with the discovery that many individuals are not truly castrate or hormone refractory (1, 5), we elected to use high-dose chemotherapy to observe if this could be used as a treatment option. Following our recent data, we also wished to specifically observe whether changes in biomarkers (PSA or CTCs) at 1 month could predict survival (21). We found that responses in patients with heavily pretreated CRPC could be induced by our protocol, and that in those individuals with increased CTCs at the start of therapy, a rapid
decrease was associated with a survival benefit. In the future, this can be used to select those individuals more likely to respond, thus avoiding toxicities. Furthermore, many individuals subsequently received further hormonal therapy and docetaxel.

The administration of melphalan and whole blood stem cell reinfusion was too toxic for routine use but we were able to deliver it with considerable support. It was possible to escalate the dose of melphalan to a cumulative dose of 180 mg/m². Compared with conventional doses of melphalan it was possible to deliver 22.5 mg/m²/wk, a 3- to 4-fold intensification over the standard chemotherapy (5–7.5 mg/m²/wk). The short high doses of lenograstim led to predictable recovery of neutrophils, and there was no suggestion that this became less likely as doses were increased. Unlike many other attempts to support dose intense chemotherapy using whole blood, the use of high-dose lenograstim before the first cycle allowed a large dose of melphalan to be given on the first cycle. Although it has been shown that whole blood progenitors will support multiple cycles of chemotherapy allowing dose density to be increased, this has never been shown previously with melphalan. The dose to take forward for a formal phase 2 study would seem to be the highest dose (it was not dose limiting), however the 4th cycle was associated with prolonged platelet recovery, and the median CD34 count had decreased before this cycle substantially therefore omitting would appear to have the advantage of decreasing toxicity (hospital admissions as well as blood product use) and further shorten the treatment.

Hematologic toxicity was considerable but was generally rapidly reversible and the use of prophylactic itraconazole and ciprofloxacin made it possible to manage most patients entirely as out patients. The treatment-related death from invasive pulmonary aspergillosis was indicative however of the degree of potential immunosuppression from this approach and therefore patients require careful monitoring when they are out of hospital. The treatment had the advantage of being completed in a short period of time (8 weeks as compared with the standard 30 weeks for 10 cycles of docetaxel). In addition, it was possible to give docetaxel following therapy. The use of fixed periods of high-dose

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<th>Table 3. Toxicity per cycle</th>
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<td>Infection</td>
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<th>Table 4. Pain scores</th>
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NOTE: Raw scores were standardized using a linear transformation, so that scores range from 0 to 100; a higher score represents a worse level of symptoms.
lenograstim allowed predictable blood count recovery; to our knowledge this has not been previously shown.

The rapid response in pain was very encouraging and it was impressive that a statistically significant improvement in pain occurred within 2 weeks of the start of treatment and that this was maintained, showing the efficacy for this therapy. The decision to stop hormone therapy during chemotherapy and only restart in the face of progression was controversial but the subsequent response to hormone rechallenge was encouraging. It is interesting that although symptom response occurred early, PSA response was delayed and often the PSA decline did not start until after the treatment was completed.

The use of CTCs to monitor response to such an intensive treatment was clearly shown and importantly this could be used early. Patients with less than 5 CTCs/7.5 mL had a numerically higher survival. Where CTCs were detected, reductions occurred rapidly with responses being seen within 2 weeks. These patients who showed this response also had numerically higher survival times. CTCs may be useful in future to help decide which patients should stop this therapy early as their changes were much more rapid than PSA. This supports our previous work in which we developed an easy to use prognostic index to identify those individuals with a prolonged survival within 1 month of starting therapy using PSA (21), however in this case the use of intensive chemotherapy followed by reintroduction of hormonal treatment made early changes in PSA much less useful. The principle of early identification of response to a therapy is of particular importance in managing CRPC—in which the number of options has expanded, allowing a change to an alternative and minimizing toxicity. In this intensive approach, CTCs seemed particularly well suited while with hormone therapy PSA remains important again potentially allowing responding patients to be identified within 4 weeks of starting therapy. The decision to withdraw hormone therapy during this study was controversial, while it is not possible to say that reinduction of endocrine sensitivity occurred the response to rechallenge particularly with dexamethasone and diethylstilbestrol was interesting and is worthy of further study.

Two patients failed to mobilize stem cells in response to the initial high-dose lenograstim and both of these had low CD34 counts in the peripheral blood following lenograstim before the first dose of melphalan. Both patients had prolonged neutropenia as would be expected, and this led to a protocol modification to ensure there was an adequate number of CD34 cells in peripheral blood before the administration of the first cycle of melphalan. Interestingly, both individuals had relatively prolonged time to progression (5.7 and 3.4 months). The CD34 cell count with the second and subsequent courses of melphalan did not seem to be predictive of the duration of marrow suppression. Some patients did experience prolonged thrombocytopenia after the 4th cycle, and further studies using this approach might show reduced toxicity if the number of cycles is cut from 4 to 3.

Limitations here include the sample size and the fact that prostate cancer, like all cancer, is a heterogeneous disease and many in this study had a particularly poor prognosis reflected in their short survival predicted by the Memorial Sloan-Kettering Cancer Center scoring system based on hemoglobin, PSA, LDH, alkaline phosphatase, albumin, Karnofsky performance status, and current age. The current role of chemotherapy in the management of CRPC is taxane dominated; alkylating drugs have not been given much consideration in recent years. The rapid response in terms of CTCs, and pain control suggests that they may be useful though our approach was toxic. The short duration of therapy and the ability to deliver docetaxel at a later date makes this approach more attractive and justifies its further exploration.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: J. Shamash, T. Powles, J. Stebbing.
Development of methodology: J. Shamash, J. Jacob, J. Stebbing.
Acquisition of data: J. Shamash, J. Jacob, K. Mutsvangwa, J. Stebbing.
Analysis and interpretation of data: J. Shamash, T. Powles, P. Wilson, J. Stebbing.
Writing, review, and/or revision of the manuscript: J. Shamash, S. Agrawal, K. Mutsvangwa, J. Stebbing.
Administrative, technical, or material support: K. Mutsvangwa, P. Wilson, J. Stebbing.
Study supervision: J. Shamash, J. Stebbing.

Acknowledgments
The authors thank the Orchid Cancer Appeal for their support in funding research nurses and supporting trial management and the input of Chugai Pharma for an unrestricted grant to part fund consumables.

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Received December 21, 2011; revised February 17, 2012; accepted February 17, 2012; published OnlineFirst March 5, 2012.

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Clin Cancer Res 2012;18:2352-2359. Published OnlineFirst March 5, 2012.

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