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Intensified Chemotherapy with Dexrazoxane Cardioprotection in Newly Diagnosed Non-Metastatic Osteosarcoma: A Report from the Children's Oncology Group

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Abstract

Background—Although chemotherapy has improved outcome of osteosarcoma, 30–40% of patients succumb to this disease. Survivors experience substantial morbidity and mortality from anthracycline-induced cardiotoxicity. We hypothesized that the cardioprotectant dexrazoxane would 1) support escalation of the cumulative doxorubicin dose (600 mg/m²) and 2) not interfere with the cytotoxicity of chemotherapy measured by necrosis grading in comparison to historical control data.⁹

Procedure—Children and adolescents with non-metastatic osteosarcoma were treated with MAP (methotrexate, doxorubicin, cisplatin) or MAPI (MAP/ifosfamide). Dexrazoxane was administered with all doxorubicin doses. Cardioprotection was assessed by measuring left ventricular fractional shortening. Interference with chemotherapy-induced cytotoxicity was determined by measuring tumor necrosis after induction chemotherapy. Feasibility of intensifying therapy with either high cumulative-dose doxorubicin or high-dose ifosfamide/etoposide was evaluated for ‘standard responders’ (SR, <98% tumor necrosis at definitive surgery).

Results—Dexrazoxane did not compromise response to induction chemotherapy. With doxorubicin (450–600 mg/m²) and dexrazoxane, grade 1 or 2 left ventricular dysfunction occurred in 5 patients; 4/5 had transient effects. Left ventricular fractional shortening z-scores (FSZ) showed minimal reductions (0.0170 ± 0.009/week) over 78 weeks. Two patients (<1%) had secondary leukemia, one as a first event, a similar rate to what has been observed in prior trials. Intensification with high-dose ifosfamide/etoposide was also feasible.

Conclusions—Dexrazoxane cardioprotection was safely administered. It did not impair tumor response or increase the risk of secondary malignancy. Dexrazoxane allowed for therapeutic intensification, increasing the cumulative doxorubicin dose in SR to induction chemotherapy. These findings support the use of dexrazoxane in children and adolescents with osteosarcoma.

INTRODUCTION

Chemotherapy for osteosarcoma has increased the 3–5 year event-free survival (EFS) from 15–20% with amputation alone to more than 60% with chemotherapy and surgical excision.^{1,2} Multiagent regimens may include doxorubicin, cisplatin, high-dose methotrexate and ifosfamide.^{1–8} Tumor necrosis evaluated in surgical specimens after induction chemotherapy, is a well-documented predictor of long-term outcome in osteosarcoma;⁹ patients with >90% tumor necrosis after induction chemotherapy have 65–80% 5-year EFS versus 40–50% EFS for those with <90% tumor necrosis.^{1–8} These data suggest need to improve treatment efficacy, especially in the latter cohort.

Doxorubicin is a major therapeutic agent for osteosarcoma. EFS is lower in regimens with lower cumulative dose or dose-intensity.^{10–11} Additional therapeutic efficacy might be garnered by increasing cumulative doxorubicin dose but perceived cardiac risk has precluded such investigations. Cumulative doxorubicin doses (450 mg/m²) currently used in the U.S.^{1–2} to treat osteosarcoma are associated with acute cardiomyopathy during chemotherapy, late cardiomyopathy in subsequent decades, and death. After 300–450 mg/m² of doxorubicin, the incidence of cardiomyopathy is significant^{12–16} with systolic

dysfunction in more than 25% of patients beyond 15 years.¹⁵ Many long term survivors are still young (40–50 years old) and at risk for cardiac deterioration over the ensuing decades.

Dexrazoxane, a cardioprotectant, protected the heart and allowed for administration of higher cumulative doxorubicin doses in women with breast cancer.¹⁷ In a study that randomized children with osteosarcoma to dexrazoxane versus no dexrazoxane, the dexrazoxane treated cohort maintained higher left ventricular fractional shortenings and received more doxorubicin.¹⁴ Wexler et. al. showed that dexrazoxane reduced acute cardiotoxicity in young patients with sarcoma but cohort size limited the assessment of oncological efficacy.¹⁸ Dexrazoxane also provided cardioprotection without affecting oncological efficacy in children with leukemia.¹⁹

We initiated report the results of this trial (P9754), comprised of 3 pilot studies delivered sequentially. The individual pilot trials provided information on the safety of intensifying therapy for ‘standard responders’ (SR: <98% tumor necrosis after induction chemotherapy) with either higher cumulative dose doxorubicin or with the high-dose ifosfamide/etoposide^{20–23}. The study was also designed to evaluate the safety and feasibility of adding dexrazoxane to both standard and intensified chemotherapy regimens for patients with osteosarcoma. We hypothesized that dexrazoxane 1) would support the escalation of the cumulative doxorubicin dose (600 mg/m²) and 2) would not interfere with the cytotoxicity of chemotherapy as measured by necrosis grading in comparison to historical control data.⁹

METHODS

Patient Eligibility

There were 242 patients <31 years old with newly diagnosed, untreated biopsy-proven intermediate or high-grade osteosarcoma without metastasis who were eligible for and enrolled on P9754. Those with low-grade osteosarcoma, parosteal or periosteal sarcoma, Paget’s disease, non-resectable tumors or tumors that might result in a marginal or intralesional resection were ineligible. Eligibility was confirmed by central pathology review. Written informed consent was obtained from the patient or his/her legal guardian according to local institutional review board guidelines.

Study Design

Three pilot regimens were tested sequentially (see Figure 1). Induction therapy consisted of two cycles of MAP (methotrexate, doxorubicin, cisplatin) on pilot 1 or MAPI (MAP with ifosfamide) on pilots 2 and 3. The chemotherapy delivered during induction on POG8651 was identical in dose and timing to that used in pilot 1 of this trial. Pilots 2 and 3 included one dose of ifosfamide instead of one of the cisplatin doses, but was otherwise identical to pilot 1. All doxorubicin was given with dexrazoxane. Definitive surgery, usually limb preservation, was performed at week 11. We evaluated necrosis grading by group (as noted above), hypothesizing equal necrosis across groups. Allocation to augmented therapy was based on the response to induction therapy.

Necrosis Grading

Assessment of necrosis was made by the institutional pathologist. A cross-section through the major and greater of two minor axes of resected tumor was prepared and the percent viable cells estimated. Good response was defined as $\leq 2\%$ viable tumor cells and standard response as $>2\%$ viable tumor cells.

Chemotherapy

The chemotherapy administered is shown in Figure 1. Chemotherapy intensification was evaluated in patients with standard response (SR: 'standard responders'). Those with good response (GR: 'good responders') continued on MAP or MAPI. All patients received methotrexate (12 g/m^2 [maximum 20 g] $\times 10$ doses) with leucovorin, cisplatin 480 mg/m^2 ($120 \text{ mg/m}^2/\text{cycle} \times 4$), and doxorubicin 450 mg/m^2 ($75 \text{ mg/m}^2/\text{cycle} \times 6$). GR on pilots 2 and 3 received ifosfamide 27 g/m^2 ($9 \text{ g/m}^2/\text{cycle} \times 3$). SR on pilots 1 and 2 received 2 additional cycles with doxorubicin (600 mg/m^2 total). SR on pilot 3 received intensification with high-dose (14 g/m^2 per cycle) of ifosfamide (cumulative 60 g/m^2), $500 \text{ mg/m}^2 \times 3$ cycles of etoposide (total $1,500 \text{ mg/m}^2$), and filgrastim support.

Each doxorubicin dose was preceded by dexrazoxane (dexrazoxane:doxorubicin ratio 10:1). Cardiac monitoring by echocardiogram (left ventricular fraction shortening) was performed at baseline, before the 3rd, 5th, and subsequent doxorubicin-containing therapy cycles, and 3, 30, and 60 months after completing therapy. Radionuclide scans were performed for clinical indications.

Statistical Analyses

Necrosis Grading with Dexrazoxane—Patients completing induction chemotherapy (without progressive disease) and having surgical resection at week 11 were evaluable for analysis of necrosis grading. The percent of patients with GR was determined for each pilot (number of evaluable patients with GR divided by total evaluable patients $\times 100$). The hypothesis of equal necrosis grading across groups defined by pilot of study enrollment was tested using the exact conditional test of proportions. Patients who then started maintenance therapy according to protocol were also considered in the analysis of post-induction outcome.

To determine whether dexrazoxane would reduce the proportion of patients with GR to induction chemotherapy, a target value of $\leq 30\%$ of patients with GR was derived from legacy study POG8651.¹ A two-stage monitoring design required at least 12 good responders in the first pilot (60 patients) and at least 27 GRs in the first two pilots (120 patients). This monitoring would have identified therapy with dexrazoxane as having inferior GR rate with probability 98% if the true GR rate were $\leq 15\%$ and as having an acceptable GR rate with a probability of 95% if the true GR rate were $\leq 30\%$.

Toxicity Analysis—Every cycle of therapy delivered was considered in the analysis of toxicity coded according to NCI Common Toxicity Criteria V2. Serious toxicity was evaluated by the number who started a particular cycle of therapy and experienced each type of toxicity at grade ≥ 3 divided by the number of cycles delivered.

Pilot 1 and 2: Anthracycline intensification: For pilots 1 and 2, monitoring was designed to detect excess heart failure (adverse cardiac event rate of $>5\%$) with delivery of 600 mg/m^2 cumulative doxorubicin. Adverse events monitored and reported according to NCI-CTCAE V2 included changes in left ventricular fractional shortening or other measures of left ventricular function that result in early discontinuation of therapy. In addition, study specific reporting during chemotherapy included documentation of non-transient reduction (2 sequential measures) of left ventricular fractional shortening below 28% .

The study was designed to stop if 3 patients among 90 SR patients experienced clinical heart failure. This stopping rule would have identified the therapy as having an excess acute heart failure toxicity rate with probability 83% if the true acute cardiac failure rate were 5% , and an acceptable acute heart failure rate with a probability of 0.94 if the true rate were 1% . The study was amended as a result of a higher-than-expected GR rate. With only 60 SR on pilots 1 and 2, pilot 1 was reopened to accrue the additional 30 SR necessary to assess feasibility and safety of doxorubicin 600 mg/m^2 .

Changes in left ventricular fractional shortening: To maximize reliability of cardiac measurements at multiple sites, central remeasurement of original echocardiogram tracings was performed using computer digital analysis based on methodology used previously to establish normative data in children.²⁴ For study analyses, central measurements were used exclusively. Left ventricular fractional shortening values were converted to z-scores (FSZ) by taking the raw score minus the average score for an age, weight, height, and sex-adjusted normal population and dividing the difference by the population's standard deviation. Any eligible patient enrolled on pilots 1 and 2 who had at least one FSZ value obtained was considered in this analysis. The FSZ value obtained immediately after the enrollment date was taken as the baseline value. Pilot 3 patients were not shown in this analysis because doxorubicin delivery was different than in pilots 1 and 2.

A statistical model for FSZ as a function of time was fitted with all data available through week 78, regardless of when the particular FSZ values was obtained. Week 78 was approximately seven months after the nominal end of therapy for the longest treatment plan; this time limit was selected to avoid bias associated with reporting of data in those with evident cardiac toxicity. A repeated measures analysis of variance described in Appendix A was fitted to the data.

Pilot 3, etoposide/ifosfamide intensification: Fanconi syndrome was monitored in Pilot 3 as the toxicity considered most likely to limit feasibility. A glomerular filtration rate $<50 \text{ ml/min/1.73 m}^2$ without other etiology or renal tubular acidosis with phosphorous wasting requiring intravenous replacement (>3 weeks) was considered an adverse event. Events were tabulated and reported at six-month intervals.

Disease Outcome—EFS was calculated from the time from enrollment until an event (disease progression, diagnosis of second malignancy, death) or until last patient contact, whichever occurred first. Patients who did not experience an event were considered censored at last contact. Prior to August 2000, patients who had localized increased tumor size by radiography prior to surgery were considered to have experienced disease

progression. The protocol was then modified to identify increased size by radiology as disease progression only if the primary was consequently unresectable. Overall survival (OS) was calculated as the time from enrollment to death or last patient contact, whichever occurred first. Patients who did not die were considered as censored at last contact.

The prognostic effect of necrosis grading was assessed as “EFS since maintenance” and “OS since maintenance”. Only patients who completed induction therapy, had necrosis grading assessed, and received at least one day of maintenance therapy were considered in this analysis. “EFS since maintenance” was defined as time from the date of beginning maintenance therapy until disease progression, diagnosis of a second malignant neoplasm (SMN), death or last patient contact, whichever occurred first. “OS since maintenance” was the time from the date of beginning maintenance therapy to date of death or of last patient contact, whichever occurred first. These definitions were also used for comparisons between pilots.

The probability of remaining event-free as a function of time since enrollment or from the start of maintenance was calculated by the method of Kaplan and Meier.²⁵ Tests for the equality of risk of EFS were done using the log-rank methodology.²⁶ The cumulative incidence of occurrence of a second malignant neoplasm was calculated according to Prentice et. al.²⁷

RESULTS

Patients

The study was activated in September 1999 and closed February 2002. Data current to July 2008 were used for this analysis. Eleven of 253 enrolled patients were ineligible: (1) four did not have osteosarcoma; (2) four did not have valid consent; (3) two had metastatic disease and (4) one did not have disease present at study enrollment. Between September 1999 and June 2000, 60 patients enrolled on pilot 1; an additional 64 enrolled between May 2001 and October 2001. Pilots 2 and 3 respectively enrolled respectively from June 2000–November 2000 and November 2000–April 2001; each accrued 59 patients.

On pilots 2 and 3, induction outcomes for all patients and all outcomes for GR are aggregated because therapy was identical. Demographic characteristics of the eligible patients are presented in Table I.

Histological response

Histological responses, as determined by necrosis grading, for pilot 1 and pilots 2/3 (pilots 2 and 3 had identical induction therapy and are therefore grouped) met or exceeded the historically based target. Necrosis 98% was achieved by induction chemotherapy on pilot 1 and on pilots 2/3 in 31% (22–40%) and 36% (27–46%) respectively ($P=.40$).

Post-induction outcome based on necrosis grading was performed in 103, 50 and 53 patients of the 124, 59, and 59 eligible patients enrolled respectively onto pilots 1, 2, and 3. Prior to surgery, 13, 5, and 3 patients from pilots 1, 2, and 3 respectively withdrew from protocol therapy (5, 1, and 1 respectively for disease progression). Eight, 5 and 3 patients

respectively on pilots 1, 2 and 3 had surgery but did not continue protocol therapy post-operatively. (See Supplemental Figure 1 for a Cohort diagram)

Toxicity

Therapeutic intensification was achieved with acceptable toxicity. The relevant targeted toxicities and grade 3 or 4 toxicities that occurred in more than 5% of patients are shown in Table II.

CTC-version 2 toxicity based on institutional echocardiograms and/or radionuclide angiography reported grade 1 or 2 left ventricular dysfunction in 5 patients (Supplemental Table I); it was transient in at least 4 of these patients. Doxorubicin was discontinued in 2 of these patients. There was no grade 3, 4 or 5 cardiomyopathy (ventricular dysfunction). One additional patient had grade 3 serum cardiac troponin-T elevation with 600 mg/m² of doxorubicin dose without documented myocardial dysfunction.

Institutions provided data regarding non-transient changes in left ventricular fractional shortening during the therapeutic interval via mandatory study specific data reporting. Follow-up cardiac studies were performed at most institutions as standard of care but compliance with central cardiology review was less uniform; it may have been influenced by institutional commitment to the process, rather than as a patient-specific decision. Echocardiograms were submitted for central cardiology review on 150 patients; with follow-up data submitted for 104 patients. These patients form the basis for analysis of changes in the FSZ over time until week 78. Based on FSZ at the start of treatment, there was no evidence of patient selection in this analysis towards either those with existing heart issues or those who were healthier than the average unaffected population. Based on additional echocardiographic data submitted to the cardiac reference center in 104 patients, the FSZ was found to decrease in a statistically significant fashion with increasing time since enrollment. The change is -0.017 ± 0.009 of a standardized unit (a z-score of 1) per week since the start of protocol therapy or an estimated annual change of 0.9 standardized FSZ units per year. Assignment to 1) standard therapy with 450 mg/m² doxorubicin or 2) doxorubicin intensification to 600 mg/m² was unrelated to change in FSZ. Figure 2 shows data for all patients with the same rate of delivery of doxorubicin (excluding etoposide/ifosfamide intensification). There was no significant change in FSZ ($p=0.85$) after induction therapy through week 78 (data not shown).

Two secondary leukemias were reported: juvenile myelomonocytic leukemia (first event at 28 months, pilot 2) and acute myeloid leukemia (after surgically-treated relapse at 51 months post-diagnosis). This latter patient's mother had secondary leukemia after breast cancer therapy. The cumulative incidence of second malignant neoplasm six years from enrollment for the aggregate study population was 0.4%. The median follow-up for patients without an SMN-event was 57 months.

Renal dysfunction and Fanconi syndrome were rare, even on Pilot 3. Hypophosphatemia was noted in all cohorts.

Outcome (Figure 3)

Of the 242 eligible patients, 95 had experienced an analytic event as of the date of analysis: (1) 91 disease recurrence; (2) one SMN as a first event; and (3) three died without disease progression or SMN. The estimated 4-year EFS was 62% (95% CI: 56–68%) for the entire population (Figure 3A) with no statistical difference in EFS among the pilots ($P=0.40$, Figure 3B). The estimated 4-year OS was 74% (95% CI: 68–79%) for the entire population (Figure 3C), with no statistical difference in OS among the pilots ($P=0.38$, Figure 3D).

Good versus Standard Response—Patients with GR were at reduced risk for an EFS-event and for OS when compared with SR patients (Figure 3F,G). Three year OS was 93% (95% CI 83–97%) for Good Risk patients vs. 75% (95% CI 67–82%) for Standard Risk Patients. Three year EFS was 81% (95% CI 70–89%) for Good Risk patients and 58% (95% CI 49–66%) for Standard Risk patients.

For patients with SR, there was no statistical difference in EFS or OS among the pilots (Figures 3C, 3E).

DISCUSSION

Doxorubicin dose intensity remains a key factor in the successful therapy of osteosarcoma^{10,11} but anthracycline-induced cardiomyopathy^{12–16} has severely impacted long-term health outcomes and limited the feasibility of further doxorubicin intensification. Methods to reduce cardiotoxicity are critical to maximize efficacy of doxorubicin treatment. Although continuous infusion may provide limited cardioprotection in adults,²⁸ no cardioprotection has been noted in children with leukemia²⁹ or osteosarcoma.²

In this study, dexrazoxane did not interfere with the tumor cytotoxicity of pre-operative induction chemotherapy. The percent of patients achieving a GR (>98% tumor necrosis) was similar or better than that of historical controls receiving therapy without dexrazoxane. This evidence supports the conclusion that dexrazoxane is unlikely to reduce the oncologic efficacy of doxorubicin treatment in osteosarcoma. We did not see an improvement in outcome for patients on this trial by augmenting therapy, but we also did not show any changes in outcome in terms of OS or EFS on this trial for GR patients who received standard therapy. This is also suggestive of a lack of impact of dexrazoxane on cytotoxicity.

Trials using bolus dose doxorubicin for osteosarcoma, often in lower doses, report a substantial incidence of significant acute cardiotoxicity. Postma et. al. reported that 4 of 31 had cardiomyopathy requiring cessation of doxorubicin.¹² Bacci et. al. reported severe cardiotoxicity in 6 of 164 patients; 5 events occurred within 12 weeks of completing therapy.³⁰ We did not see this degree of acute cardiotoxicity in patients receiving either standard (450 mg/m²) or intensified (600 mg/m²) doxorubicin.

Severe left ventricular dysfunction (grade 3) was not noted on our trial. Five grade 1 or 2 cardiac toxicities occurred; 4 were transient. The significance of a grade 3 serum cardiac troponin-T elevation is unknown. Left ventricular fractional shortening declined minimally over time, but patients remained asymptomatic. The estimated annual decrease in

standardized FS was 0.9 in the first year of therapy, the time period after doxorubicin, when most significant reductions in the first decade are reported. Based on Ewing sarcoma data, minimal early reductions in FS are not expected to be associated with late cardiotoxicity.¹⁵ Although central cardiology review was incomplete, any bias in collection that would have been based on individual patient factors (rather than on feasibility barriers at a specific institution) would likely favor submission of cardiac studies on patients considered to be at higher risk. Additional follow-up of P9754 patients will be needed to ascertain the long-term impact of dexrazoxane.

Our study clearly shows the feasibility of administering high cumulative dose doxorubicin. These small pilots were not designed to evaluate the efficacy of doxorubicin intensification to 600 mg/m²; EFS and OS on P9754 were comparable to other regimens. Large randomized trials would be needed to determine whether escalation of cumulative doxorubicin dose is beneficial in osteosarcoma.

We also found that higher ifosfamide dose with etoposide could be added to standard therapy safely. Standard responders on pilot 3 received a cumulative doxorubicin dose of 450 mg/m² and ifosfamide 60 g/m² without evidence of cardiotoxicity or other unexpected toxicity. The recently closed European and American Osteosarcoma study evaluated this therapeutic intensification without the use of dexrazoxane.³¹

Dexrazoxane did not adversely affect early therapeutic response. With dexrazoxane, the risk of acute cardiomyopathy was strikingly low and there was no evidence for an increase risk for secondary leukemia. In contrast to other osteosarcoma trials^{1,4} in which secondary leukemia was reported in 1% to 2% of patients, secondary leukemia occurred in only two P9754 patients (<1%), including one with a family history of secondary malignancy.

The European Medicines Agency has prohibited access to dexrazoxane in the pediatric population due to concerns over the risk of SMNs³², a decision that was apparently based primarily on the non-statistically significant increase in SMNs observed in a single Hodgkin lymphoma trial³³ that administered three topoisomerase inhibitors simultaneously. Data presented here add to a growing body of literature^{34,35} that does not demonstrate a significantly greater risk of SMNs in patients exposed to dexrazoxane. Although another decade must pass before we can confirm that dexrazoxane has sufficiently abrogated long-term risk of cardiomyopathy, our results provide a reason for optimism in patients with osteosarcoma. We believe that these data support the use of dexrazoxane for all children who require anthracycline therapy for the treatment of osteosarcoma. Access to dexrazoxane may also be critically important for the long-term health of other children requiring high-dose anthracycline therapy to cure cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest: S Lipshulz has been a consultant for Clinigen. PM has been a consultant to Takeda, Eli Lilly and Har, Wagner, LLP, has stock in Amgen, Jazz Pharmaceuticals, Mednax, Novartis, and Sigma Aldrich, and his spouse/partner has speaking engagements or CME with Boehringer Ingelheim, Pharmacy times and France Foundation.

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Pre-Operative Therapy											
Week	1	2	3	4	5	6	7	8	9	10	11
Pilot 1	aP			M	M	aP			M	M	Surgery
Pilot 2, 3	ai			M	M	aP			M	M	Surgery
Post-Operative Therapy: Good Response											
Week	13	14	15	16	17	18	19	20	21	22	23
Pilot 1	M	aP		M	aP		M	a		M	a
Pilot 2, 3	M	ai		M	aP		M	ai		M	aP
Post-Operative Therapy: Standard Response											
Week	13	14	15	16	17	18	19	20	21	22	23
Pilot 1	M	aP		M	aP		M	a		M	a
Pilot 2	M	ai		M	aP		M	ai		M	aP
Pilot 3	M	le		ai		M	aP		le	le	

Figure 1. The chemotherapy used includes ifosfamide (i): 1.8 g/m²/d × 5 days with MESNA (360 mg/m²/dose 5 daily for 5 days, high dose ifosfamide (I): 2.8 g/m²/d × 5 = 14 g/m² with MESNA (560 mg/m²/dose) 5 daily for 5 days, cisplatin (P): 60 mg/m²/d × 2 days, methotrexate (M): 12 g/m² with leucovorin 15 mg every 6 hours, doxorubicin (a): 37.5 mg/m²/d × 2 days with dexrazoxane 375 mg/m² before each dose, and etoposide (e) as 100 mg/m²/d × 5 days.

Figure 2.

Change in left ventricular fractional shortening, with time up to week 78, is shown for all patients with the same rate of delivery of doxorubicin (excluding etoposide/ifosfamide intensification). Blue squares represent all FCZ values for patients who received a total dose up to 450 mg/m² and FCZ values obtained prior to the time of augmented doxorubicin doses in SR on pilots 1 and 2. Red asterisks represent FCZ obtained after the time when more than 450 mg/m² would have been administered to SR on pilots 1 and 2.

Figure 3.

EFS and OS for P9754 are shown in 3A where the blue line represents EFS and the red dashed line represents OS. Figure 3B shows EFS by pilot since maintenance ($p=0.40$). The blue line represents Pilot 1, the red dashed line represents Pilot 2, and the green dashed and dotted lines represent pilot 3. Figure 3C shows the EFS of SR patients by pilot since maintenance ($p=0.560$). The blue line represents Pilot 1, the red dashed line represents Pilot 2, and the green dashed and dotted lines represent pilot 3. Figure 3D shows Overall Survival by pilot since maintenance ($p=0.38$). The blue line represents Pilot 1, the red dashed line represents Pilot 2, and the green dashed and dotted lines represent pilot 3. Figure 3E shows Overall survival of SR patients by pilot since maintenance ($p=0.69$). The blue line represents Pilot 1, the red dashed line represents Pilot 2, and the green dashed and dotted lines represent pilot 3. Figure 3F shows EFS since maintenance for Good vs. Standard Responders ($p=0.001$). The blue line represents good response and the red dashed line represents standard response. Figure 3G shows OS since maintenance for Good vs. Standard Responders ($p=0.002$). The blue line representing good response and the red dashed line representing standard response.

Table I**Patient characteristics**

Demographic characteristics of patients on P9754 are shown.

	Pilot 1 (N=124)	Pilot 2 (N=59)	Pilot 3 (N=59)
Age at Enrollment (years)			
Median (range)	13 (4, 30)	13 (4, 28)	14 (3, 27)
0–11	39 (31%)	20 (34%)	20 (34%)
12–14	36 (29%)	17 (29%)	14 (24%)
15+	49 (39%)	22 (37%)	25 (42%)
Gender			
Male	73 (59%)	32 (54%)	34 (58%)
Female	51 (41%)	27 (46%)	25 (42%)
Ethnicity			
White	89 (72%)	39 (66%)	37 (63%)
Hispanic or Latino	7 (6%)	5 (8%)	6 (10%)
African American	23 (19%)	7 (12%)	9 (15%)
Asian	2 (2%)	5 (8%)	3 (5%)
Native Hawaiian or Pacific Island	0 (0%)	0 (0%)	1 (2%)
American Indian or Alaska Native	0 (0%)	1 (2%)	1 (2%)
Other	1 (1%)	0 (0%)	2 (3%)
Not Reported	2 (2%)	2 (3%)	0 (0%)

Table II**Toxicity**

Toxicity of therapy on P9754 is shown.

Grade 3 or Greater	Induction Toxicity All Patients		Post-surgery Toxicity GR		Post-Surgery Toxicity SR: Intensified Regimens		
	Pilot 1 N=123	Pilot 2/3 N=118	Pilot 1 N=32	Pilot 2/3 N=39	Doxorubicin 600mg/m ² Pilot 1 N= 71	Doxorubicin 600mg/m ² Pilot 2 N=30	Etoposide Ifosfamide Pilot 3 N=19
Targeted Toxicities ---PERCENT							
Left Ventricular Function	0	0	0	0	0	0	0
Ventricular Arrhythmia	0	0	0	0	0	0	0
Cardiac Troponin	0	0	0	0	1.4	0	0
Hearing	0	0	0	7.7	1.4	3.3	0
Hypophosphatemia	5.7	3.4	3.1	12.8	14.1	20.0	20.6
Creatinine	0.8	1.7	0	0	1.4	0	0
Hemoglobin (Hgb)	48.0	39.0	65.6	71.8	71.8	60.0	67.6
Leukocytes (total WBC)	55.3	66.9	62.5	82.1	69.0	80.0	76.5
Neutrophils/Granulocytes	74.8	73.7	75.0	94.9	81.7	90.0	82.4
Platelets	42.3	39.8	78.1	94.9	85.9	80.0	85.3
Wound-infectious	2.4	6.8	9.4	5.1	8.5	6.76.7 0	11.8
Anorexia	8.1	0.8	6.3	5.1	4.2	10.0	11.8
Constipation	0	0	0	5.1	4.2	0	2.9
Diarrhea	0.8	0	3.1	5.1	4.2	3.3	5.9
Dysphagia, Esophagitis	1.6	2.5	3.1	2.6	9.9	0	2.9
Nausea	17.9	11.0	9.4	10.3	16.9	10.0	5.9
Stomatitis/Pharyngitis	21.1	18.6	25.0	23.1	32.4	43.3	29.4
Vomiting	28.5	16.1	18.8	12.8	15.5	13.3	14.7
Epistaxis	0	0	0	7.7	2.8	6.7	11.8
Bilirubin	2.4	4.2	3.1	7.7	1.4	0	0
SGOT (AST)	27.6	29.7	25.0	15.4	18.3	16.7	17.6

Grade 3 or Greater	Induction Toxicity All Patients		Post-surgery Toxicity GR		Post-Surgery Toxicity SR: Intensified Regimens		
	Pilot 1 N=123	Pilot 2/3 N=118	Pilot 1 N=32	Pilot 2/3 N=39	Doxorubicin 600mg/m ² Pilot 1 N= 71	Doxorubicin 600mg/m ² Pilot 2 N=30	Etoposide Ifosfamide Pilot 3 N=19
SGPT (ALT)	48.8	55.1	43.8	35.9	40.8	30.0	38.2
Catheter-related infection	6.5	3.4	6.3	12.8	9.9	13.3	14.7
Hypotension	1.6	0	6.3	0	2.8	3.3	2.9
Febrile neutropenia (FUO)	35.8	33.1	37.5	43.6	45.1	40.0	52.9
Infection & 3/4 neutropenia	19.5	16.1	31.3	43.6	49.3	50.0	44.1
Infection without neutropenia	7.3	6.8	12.3	10.3	9.9	13.3	11.8
Hyperglycemia	9.8	9.3	9.4	17.9	21.1	6.7	17.6
Hyperkalemia	1.6	0.8	3.1	5.1	4.2	0	0
Hypermagnesemia	3.3	2.5	0	7.7	2.8	0	0
Hypocalcemia	4.9	0.8	3.1	10.3	9.9	3.3	0
Hypokalemia	6.5	8.5	21.9	28.2	19.7	13.3	32.4
Hypomagnesemia	1.6	0	0	5.1	11.3	3.3	2.9
Hyponatremia	10.6	4.2	9.4	7.7	11.3	13.3	2.9