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Title

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Permalink

https://escholarship.org/uc/item/9s33p290

Journal

Pediatric blood & cancer, 65(5)

ISSN

1545-5009

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Publication Date

2018-05-01

DOI

10.1002/pbc.26928

Peer reviewed

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HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2018 September 13.

Published in final edited form as:

Pediatr Blood Cancer. 2018 May ; 65(5): e26928. doi:10.1002/pbc.26928.

Isolated late testicular relapse of B-cell acute lymphoblastic leukemia treated with intensive systemic chemotherapy and response-based testicular radiation: A Children's Oncology Group study

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Abstract

Background—The incidence of isolated testicular relapse (ITR) of acute lymphoblastic leukemia (ALL) has decreased with contemporary treatment strategies, but outcomes are suboptimal with a 58% 5-year overall survival (OS). This study aimed to improve outcome in patients with ITR of B-cell ALL (B-ALL) occurring after 18 months of first clinical remission using intensive systemic chemotherapy and to decrease long-term sequelae by limiting use of testicular radiation.

Procedure—Forty patients in first ITR of B-ALL were enrolled. Induction (dexamethasone, vincristine, daunorubicin, and intrathecal triple therapy) was preceded by one dose of high-dose methotrexate (MTX, 5 g/m^2). Following induction, 25 of 26 patients who had persistent testicular enlargement underwent testicular biopsy. Eleven had biopsy-proven disease and received bilateral testicular radiation (24 Gy), whereas twenty-nine did not.

Results—Overall 5-year event-free survival (EFS)/OS was 65.0 ± 8.8%/73.1 ± 8.3%, with 5-year EFS 62.1±11.0% vs. 72.7±14.4% for patients who did not receive radiation therapy (XRT) (n=29) compared with those who did (n = 11), respectively (P = 0.64). There were six second bone marrow relapses and six second ITRs. The proportion of second relapses was similar in the patients that received testicular radiation and those who did not. However, the 5-year OS was similar for patients who did not receive XRT (72.6 ± 10.2%) compared with those who did (72.7 ± 14.4%) (P = 0.85).

Conclusions—A 5-year OS rate of 73.1 ± 8.3% was obtained in children with first ITR of B-ALL occurring after 18 months of CR1 (length of first clinical remission) using intensive chemotherapy and limiting testicular radiation.

1 INTRODUCTION

Refinement of strategies used to treat children with newly diagnosed acute lymphoblastic leukemia (ALL) has continued to improve survival. However, relapse in the marrow and extramedullary sites remains problematic and most patients who relapse do not survive. Isolated overt testicular relapse is becoming distinctly less common, with an incidence of approximately 0.5–2% among males in the most recent Children's Cancer Group (CCG) ALL trials in both the standard and high-risk groups.[1–4] The incidence of testicular relapse has steadily decreased over the past two decades, attesting to the effectiveness of improved systemic therapy in the ability to eradicate disease in the testes and prevent relapse in this sanctuary site.[5–19]

The major impact of isolated testicular relapse (ITR) is the high incidence of subsequent systemic relapse, though this appears to be directly influenced by length of first clinical remission (CR1).[18–23] In POG 8304 (1983–1989), the overall 4-year event-free survival (EFS) among males with occult testicular relapse at completion of therapy was 53 ± 8%, compared to 84 ± 10% for males with late overt ITR (6 months or greater following completion of therapy).[18,19] A more recent analysis of the CCG database (CCG 1881, CCG 1882, CCG 1901, CCG 1883, CCG 1922, unpublished results) showed a trend to poorer outcome for those with CR1 < 18 months versus > 18 months (5-year EFS 43% vs. 61%, respectively), though numbers are small and do not reach statistical significance. These

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findings suggested that a different approach to treatment may be warranted for early and late ITR.

Endocrine late effects following testicular radiation are significant, with a majority of males requiring hormonal replacement at some stage for induction of puberty or continuing pubertal maturation or both.[24–29] Radiation also leads to sterility and may result in disturbed sexual function. Age (and pubertal status) at time of radiation as well the radiation dose to the testes are factors in outcome.[30–33] In light of an anticipated growing number of survivors of ITR and ALL relapse in general, consideration of significant late effects potentially impacting quality of life should be considered seriously in the decision regarding treatment.[34,35]

In this trial, we sought to determine whether testicular radiation may be able to safely be omitted while maintaining or improving EFS. The approach taken in this study was to use intensive systemic chemotherapy to improve overall EFS and to allow elimination of testicular radiation by using higher doses of methotrexate (MTX, shown in preclinical studies to penetrate the blood–testis barrier) and other drugs effective in the treatment of ITR. The Children's Oncology Group (COG) protocol AALL02P2 was designed with the primary objective to eliminate testicular radiation by further intensifying chemotherapy with proven agents that enter into the testicular interstitium in adequate cytocidal concentrations (particularly high-dose MTX [HDMTX]). Secondary objectives included the documentation of marrow minimal residual disease (MRD) at time of relapse and assessment of pretreatment MRD as it correlates with outcomes.

2 PATIENTS AND METHODS

2.1 Patients

COG protocol AALL02P2 opened to patient entry November 1, 2004 and closed to accrual January 7, 2011. This protocol was designed to treat patients with ALL and late isolated extramedullary relapse, defined as a CR1 ≥18 months. Eligibility for participation on study included age 18 months to <30 years at time of relapse, history of ALL in first bone marrow (BM) remission with isolated central nervous system (CNS) and/or testicular relapse, and length of CR1 ≥18 months from time of initial diagnosis. BM evaluation was required to be M1 by morphology (less than 5% blasts). Patients with Down syndrome were not eligible due to increased sensitivity to MTX. Testicular relapse was suspected on the basis of unilateral or bilateral testiculomegaly. Testicular biopsy was required for confirmation of relapse.

2.2 Treatment

All patients enrolled on the study received a common induction, consolidation, intensification I, reinduction, and intensification II, with concomitant prophylactic intrathecal triple chemotherapy (MTX, cytarabine, hydrocortisone) dosed by age. Maintenance therapy was stratified according to site of extramedullary relapse (Table 1). Induction for patients with ITR began with a single HDMTX (5 g/m^2) and then continued 2 weeks later with induction (vincristine [VCR], daunorubicin, dexamethasone [DEX])

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without testicular radiation. Patients with ITR and persistent clinical testicular enlargement at the end of induction underwent repeat testicular biopsy of the affected testes(is). Patients with biopsy-proven testicular leukemia at the end of induction received 24 Gy bilateral testicular radiation during consolidation, while those without testicular enlargement at end induction and those with negative biopsies did not receive irradiation. In total, patients with ITR received nine doses of HDMTX (45 g/m^2) and 4 g/m^2 of cyclophosphamide. However, prior cumulative doses of cyclophosphamide were considered and the total dose was capped at 6.4 g/m^2 to attempt preservation of testicular function.

All ITR patients received a common maintenance therapy every 10 weeks for two cycles with DEX pulses, weekly intramuscular MTX, daily oral 6-mercaptopurine alternating with 4 weekly doses of cyclophosphamide and VCR. Filgastrim was given following treatment with cytarabine and PEG-asparaginase. This was followed by a second phase of maintenance therapy (two cycles, 10 weeks each) with monthly pulses of DEX and VCR, daily oral 6-mercaptopurine, and weekly intramuscular MTX. Patients also received age-adjusted intrathecal triple chemotherapy (MTX, hydrocortisone, cytarabine) during both maintenance phases.

BM samples taken prior to initiation of treatment were assessed for MRD using flow cytometry and PCR analysis for clonality (both were optional).[36] These samples were requested to be collected at the time of determination of possible marrow involvement and to be available for comparison later in the event of systemic relapse. The level of MRD also was to be correlated with EFS to ascertain its predictive value.

2.3 Study design and statistical methods

Primary endpoints were EFS and overall survival (OS) from the time of enrollment, as compared to historical outcomes. EFS was calculated as the time from enrollment to first event (induction death, induction failure, relapse at any site, second malignant neoplasm, or remission death from any cause) or last contact, and OS was defined as the time from enrollment to death from any cause or last contact. Five-year EFS and OS are presented in this report. OS rates were estimated using the Kaplan–Meier method and the corresponding standard deviations were obtained with Peto's method.[37,38] The two-sided log-rank test was used for comparison of survival curves between groups. *P*-values < 0.05 were considered statistically significant. Data were frozen in September, 2016.

3 RESULTS

3.1 Patients characteristics

A total of 40 patients were enrolled, with a median age at the time of initial diagnosis and enrollment on AALL02P2 of 4.6 years and 8.9 years, respectively. Most patients (75%) had been classified as standard risk (age > 1 and < 10 years and initial WBC < 50,000/μl) using the NCI criteria at the time of their initial diagnosis of ALL (26 standard risk, nine high risk, one infant, and four unknown). High-risk patients are those with age ≥ 10 years or WBC ≥ 50,000/μl at diagnosis.[39] Most patients had received front-line therapy according to standard CCG or POG ALL protocols. The demographics are presented in Table 2.

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Of 166 eligible patients with either isolated CNS or testicular relapse enrolled on AALL02P2, 42 of these patients with isolated late testicular relapse were enrolled on this protocol stratum. Of these, 40 patients had B-ALL and two T-ALL: this analysis is limited to those patients with B-ALL. All patients had biopsy-proven testicular relapse.

3.2 Response to therapy

As per protocol design, only patients who did not have a complete response to induction chemotherapy received testicular radiation. Patients with resolution of testicular enlargement at the end of induction therapy were considered to have a complete response. Those with persistent testicular enlargement at the end of induction therapy were required to undergo biopsy to assess response. Of the 40 B-ALL ITR patients, 26 had persistent testicular enlargement and 25 had a repeat testicular biopsy of the enlarged testes (is) (see CONSORT diagram; Figure 1). Twelve of them had a positive biopsy indicating persistence of testicular leukemia, and, of these, 11 received testicular radiation per protocol guidelines (the remaining patient went off study, see below). Consequently, 29 patients (73% of enrolled patients) did not receive testicular radiation and their therapy was limited to the intensive chemotherapy regimen outlined in Table 1. Of the two patients with T-ALL, one patient died 1 year after enrollment and the second patient remains alive at the time of last contact (4.83 years from enrollment).

Fourteen events occurred including 12 relapses, one death in remission, and one second malignant neoplasm (Table 3). Of the 12 patients experiencing a subsequent relapse, six had a second ITR and six had a systemic (BM) relapse. One of these patients experienced early BM relapse and was removed from protocol therapy after induction (this patient was considered unevaluable per protocol guidelines and not included in analysis of EFS and OS based). This patient had a testicular response and did not receive radiation. Among those patients who suffered a subsequent systemic relapse, two occurred in the group that did not receive testicular radiation (for a total of three patients) and three in patients that received testicular radiation due to persistence of biopsy-proven testicular leukemia at the end of induction therapy.

None of the 11 patients that received testicular irradiation had a second testicular relapse. Among the 29 patients who did not receive testicular irradiation, 23 (80%) did not have a second testicular relapse, while six (20%) had a testicular relapse. Fourteen patients had clinical resolution of testicular leukemia at the end of induction, and three of these had a second testicular relapse. Thirteen patients had persistent testicular enlargement at end of induction but a negative biopsy, and three of these had a second testicular relapse.

A secondary objective of this study was to determine the presence of BM involvement detectable as MRD at the time of isolated extramedullary relapse. MRD was measured in the BM at the time of diagnosis of ITR using previously described flow cytometry techniques.[36]

3.3 EFS

Five-year EFS for B-ALL patients with ITR was 65.0 ± 8.8%, whereas 5-year OS was 73.1 ± 8.3% (Figure2A and 2B). When patients were stratified by treatment with testicular radiation, 5-year EFS was 72.7 ± 14.4% for those who received testicular radiation and 60.7

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± 11.5% for patients who did not. In comparison, 5-year OS for patients with ITR treated with testicular radiation was 72.7 ± 14.4% compared to 71.4 ± 10.6% for patients who did not receive testicular radiation (Figure2C and 2D). For those few patients who had detectable systemic MRD (≥0.01%) at the time of diagnosis of ITR, 5-year EFS (33.3 ± 27.2% vs. 68.0 ± 11.1%; $P = 0.05$) and OS (33.3 ± 27.2% vs. 73.7 ± 10.5%; $P = 0.03$) were significantly worse compared to those who did not.

MRD was measured in 29 patients at diagnosis of testicular relapse, with the sensitivity at the level of 0.01% in 28 patients and at the level of 0.1% in 29. Subsequent relapse occurred in two (both BM) of the three patients with positive MRD (between 0.01% and 0.1%) and in seven (two BM and five testicular) of the other 26 patients with negative MRD.

3.4 Toxicity

Toxicities in this cohort where those expected following 12 months of intensified systemic chemotherapy. From a total of 29 patients who entered and received maintenance chemotherapy, 26 of them were delayed by 8weeks or more (≥14 months from study entry). Therefore, although only one toxic death (infection) was seen in this cohort, the intensity of this regimen led to multiple delays in therapy.

The most common toxicity experienced by patients on this trial was myelosuppression, with 31 and 15 episodes of grade 3/4 neutropenia and thrombocytopenia, respectively (Table 4). Myelotoxicity was more severe following the phases of therapy that included high-dose cytarabine. There were 26 episodes of febrile neutropenia, 64% of which occurred during consolidation and intensification II. Although the incidence of febrile neutropenia was considerable, only one episode of sepsis occurred, nevertheless most patients (26/29) who entered and received maintenance chemotherapy experienced significant delays highlighting the intensity of the regimen. There were a total of seven episodes (17%) of severe hypersensitivy reactions (anaphylaxis) to PEG-asparaginase. Other observed toxicities included dehydration, hyperglycemia, diarrhea, and mucosistis, all of which would be expected in an intensive multiagent chemotherapy regimen for ALL.

4 DISCUSSION

In this report, we describe 40 children with first late (CR1 ≥ 18 months) ITR of B-ALL treated with a regimen of intensive chemotherapy in which testicular radiation was avoided in two-thirds of patients who had resolution of testicular leukemia at the end of induction. The primary objective of the study was to assess efficacy of the intensive regimen without testicular radiation therapy. Twenty-nine of the 40 patients with ITR B-ALL did not get irradiated while 11 got irradiated. The decision to irradiate was based on whether testicular enlargement was resolved at end of induction, if not then a biopsy was performed and patients with positive biopsy were irradiated. The nonirradiated group (except for one patient) did not have confirmation via a negative biopsy. The study was not formally designed for such a comparison and the sample sizes are small. Nevertheless, this approach demonstrated efficacy with a 5-year EFS of 65.0 ± 8.8% and 5-year OS of 73.1 ± 8.3% for the entire cohort. More importantly, although we saw a nonstatistically significant trend to improved 5-year EFS for those who received testicular radiation compared to patients who

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did not (72.7±14.4% vs. 62.1 ± 11.0%, $P = 0.64$), 5-year OS for patients with ITR treated with or without testicular radiation was identical (72.7 ± 14.4% compared to 72.6 ± 10.2%, respectively).

Therefore, using a regimen that included 12 months of intensive systemic chemotherapy using drugs known to penetrate the blood–testis barrier followed by maintenance therapy, we were able to avoid testicular radiation in two-thirds of patients. This led to the avoidance of potential long-term toxicity associated with testicular radiation in patients who exhibited clearance of testicular leukemia at the end of induction therapy, without decreasing OS.

Prior to embarking on this clinical trial we were intrigued with a report from The Dutch Late Effects study group on outcomes in five males with late ITR in which testicular radiation (previously a mainstay of treatment for ITR in addition to systemic retreatment) was omitted.[40] Our study sought to answer the question if testicular radiation, a long standing component of retreatment for ITR, can be safely omitted in a subset of patients with late ITR (defined as ≥ 18 months from initial diagnosis). Indeed, in 40 males with ITR (to our knowledge, the largest reported cohort of patients with ITR treated with a uniform approach), we were able to avoid testicular radiation in the subset of patients (72%) who cleared their testicular leukemia by the end of induction.

The overall strategy of using a regimen of intensive systemic chemotherapy was based on past experience indicating that most treatment failures in ITR patients are due to a subsequent systemic relapse. A similar approach by POG investigators had been successful in children with first isolated CNS relapse of ALL.[41] A cornerstone of the current regimen was the use of drugs known to penetrate the blood–testis barrier, particularly those proven agents that cross into the testicular interstitium in adequate cytocidal concentrations (HDMTX) as a strategy to avoid testicular radiation. We also limited the cumulative total dose of cyclophosphamide to minimize fertility-related long-term toxicity particularly for the subgroup that did not require testicular radiation. Although at this time we do not have long-term data to support the effectiveness of this approach on the patient's reproductive health, neuroendocrine function has been previously evaluated in males receiving intermediate-dose MTX, with preservation of function and achievement of sexual maturity.[40,42]

A secondary objective of this study was to determine if isolated extramedullary relapse of ALL is truly isolated to the affected extramedullary sites or the first clinical manifestation of a broader systemic relapse. A total of 29 BM samples obtained at the time of ITR were available for MRD analysis using flow cytometry. We found evidence of systemic involvement at the time of ITR in only three patients. These findings contrast with previous reports using PCR-based detection methods for MRD determination in which most patients were found to have MRD positivity in the BM at the time of extramedullary relapse.[43,44] It is unclear at this time what the basis for this discrepancy is, although it is possible that it reflects the higher level of sensitivity of PCR-based methods, differences in the populations of patients studied or differences in therapy when comparing cohorts across different treatment eras, or a combination of these factors.

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This intensive multiagent regimen was well tolerated in this cohort. As expected, myelosuppression leading to episodes of febrile neutropenia were the most common toxicities. The high incidence of myelosuppression led to ≥8 weeks delays in entering maintenance chemotherapy for many patients on this study. Based on EFS comparisons with historical controls, these delays did not impact negatively on EFS or OS for ITR patients treated on this study. Only one toxic death was observed in this group of ITR patients due to cytomegalovirus pneumonitis complicated with multiorgan failure. In addition, seven (17%) patients experienced severe hypersensitivity reactions (anaphylaxis) in this regimen that uses intensive dosing of PEG-asparaginase. Other toxicities reported in this cohort were similar to what is usually observed for similar intensive multiagent ALL regimens.

The 5-year EFS and OS in this study demonstrate improvement over historical controls. It is important to note our analysis is confined to B-ALL patients only and historically studies have included T- and B-cell precursor ALL patients. Even though 5-year EFS was lower for those patients who did not have testicular radiation following induction chemotherapy compared to those who did (62.1 ± 11.0% vs. 72.7 ± 14.4%, respectively), this difference was not statistically significant and 5-year OS was practically identical (72.6 ± 10.2% compared to 72.7 ± 14.4%, respectively).Most important, although second ITR only occurred in the nonirradiated group, most patients were salvaged by additional chemotherapy and/or stem cell transplant. Therefore, our approach leading to avoidance of testicular radiation in a subgroup of ITR patients likely resulted in lower long-term neuroendocrine morbidity and improved reproductive health for these children. A potential disadvantage of this approach is that some of these patients required hematopoietic stem cell transplant (HSCT) as salvage therapy, and one could argue regarding the additional risks associated with HSCT. In this context, careful consideration should be given to these issues when recommending our approach to ITR patients and their families, and it is important that they consider the pros and cons of testicular radiation versus the risk of requiring HSCT as salvage therapy for those with a subsequent relapse.

In conclusion, our data demonstrate that successful treatment of first ITR of B-ALL and a CR1 of ≥ 18 months with intensive multiagent chemotherapy yielded improved 5-year EFS and OS compared to historical controls and allowed avoidance of testicular radiation in a subgroup of patients that demonstrated resolution of testicular leukemia following induction therapy. Five-year OS was comparable for patients treated with or without radiation therapy, reflecting the high salvage rate for patients who did not get testicular radiation and suffered a subsequent ITR or combined relapse. This approach has the potential to decrease long-term sequelae of testicular radiation and should be considered for males with B-ALL who suffer their first ITR.

Acknowledgments

J.C.B. is the Toppel Family Chair in Pediatric Hematology-Oncology at The University of Miami Miller School of Medicine. M.L.L. is the Benioff Distinguished Chair of Children's Health. S.P.H. is the Jeffrey E. Perelman Distinguished Chair in Pediatrics at The Children's Hospital of Philadelphia.

Funding information

St Baldrick′s Foundation

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Grant sponsor: COG Chair's Operations; Grant numbers: U10 CA98543 and U10 CA180886; Grant sponsor: COG Statistics and Data Center; Grant numbers: U10 CA098413 and U10 CA180899.

Abbreviations

ALL	acute lymphoblastic leukemia
BM	bone marrow
CNS	central nervous system
DEX	dexamethaose
EFS	event-free survival
HSCT	hematopoietic stem cell transplant
ITR	isolated testicular relapse
MRD	minimal residual disease
MTX	methotrexate
OS	overall survival
VCR	vincristine
XRT	radiation therapy

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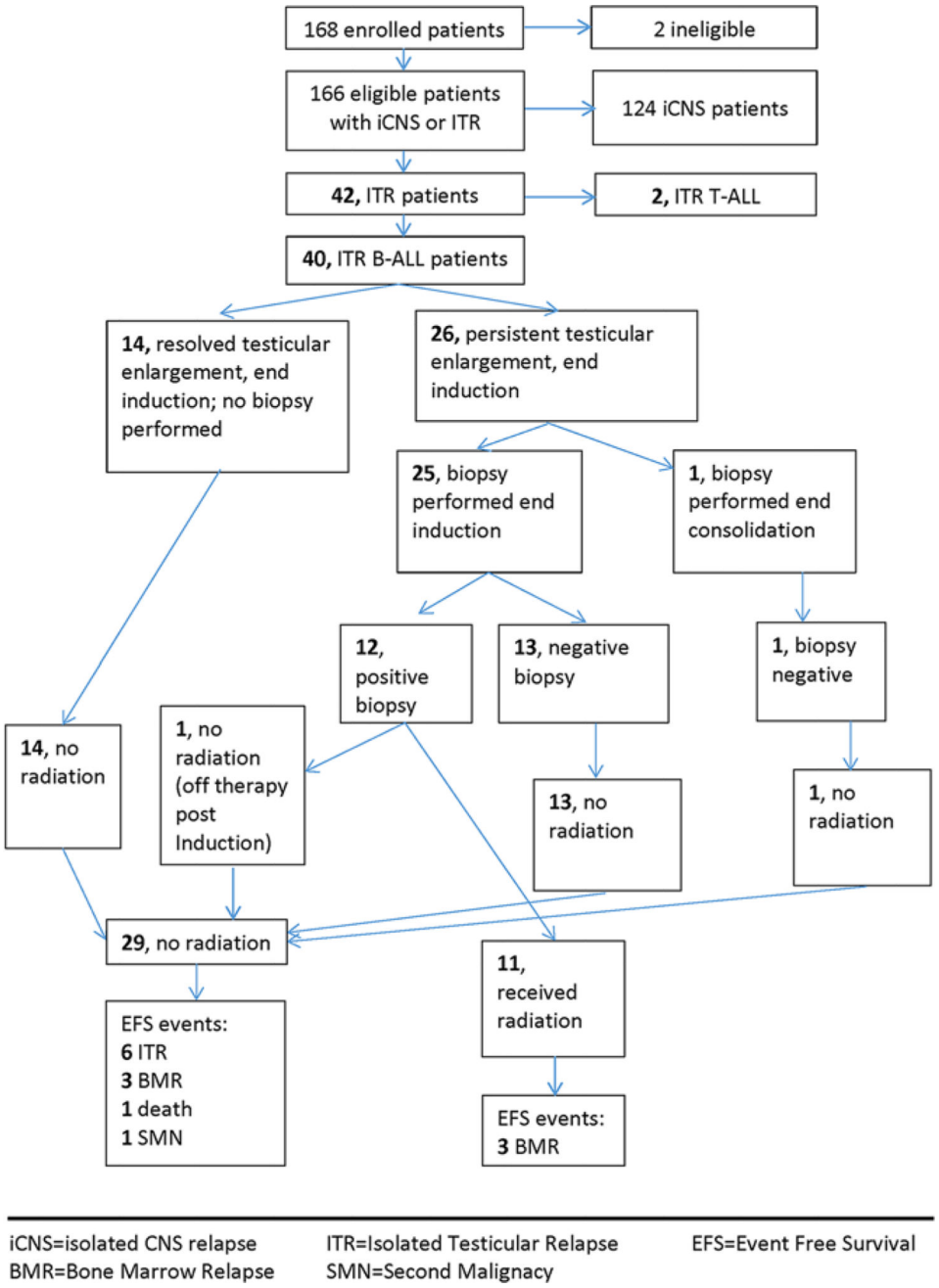

FIGURE 1.

CONSORT Diagram: Patient treatment and outcomes. Pathway followed by all patients enrolled on AALL02P2. Patients were excluded from the final analysis for ITR patients based on ineligibility (2), isolated CNS relapse (124), and T-ALL phenotype (32). The remainder 40 B-ALL ITR patients had an initial assessment of response at the end of induction therapy. Testicular biopsy positive patients received testicular radiation during consolidation therapy, whereas those with a negative biopsy did not

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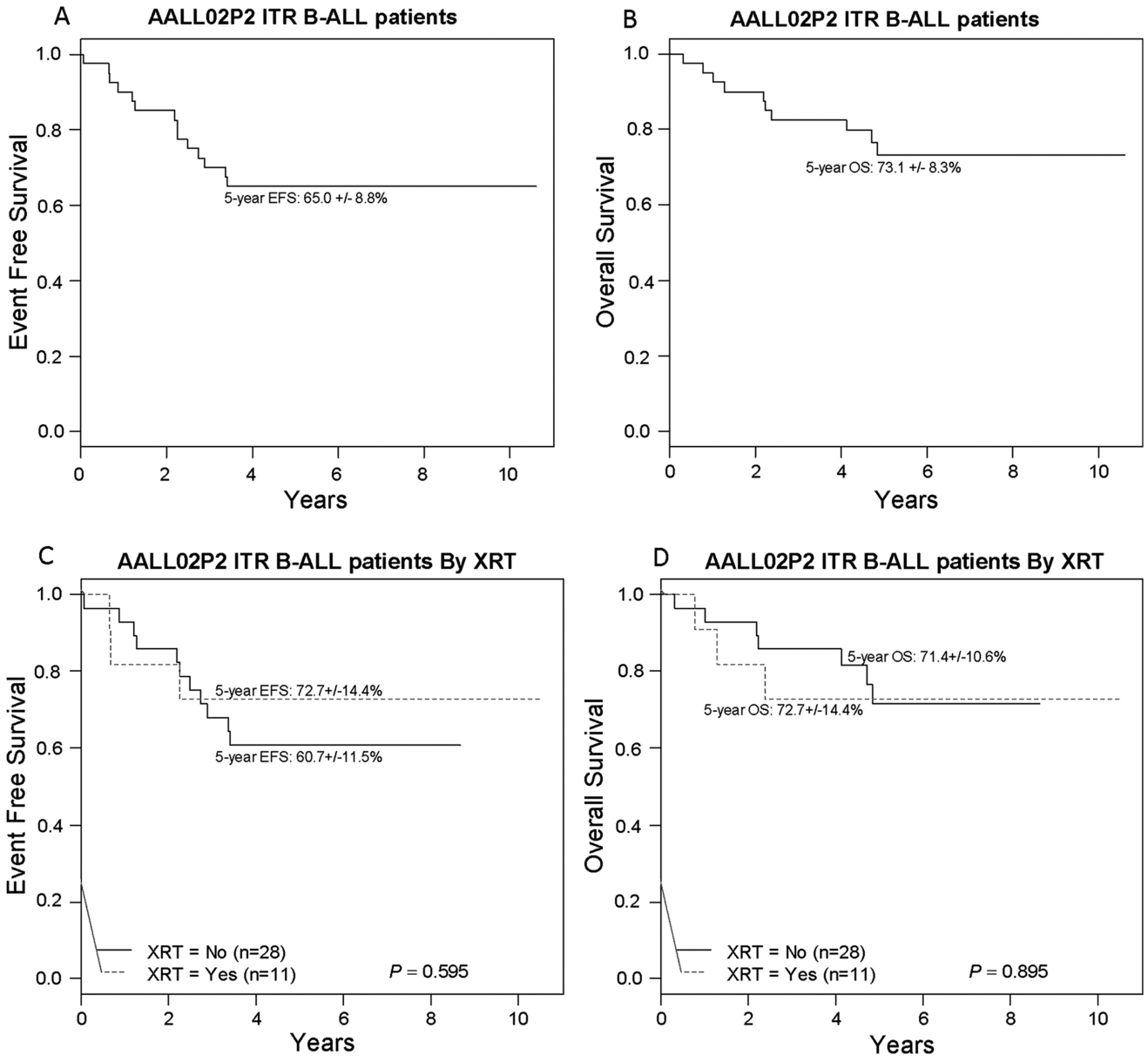

FIGURE 2.

Event-free survival (EFS) and overall survival (OS) of ITR patients with B-ALL enrolled on the Children's Oncology Group (COG) AALL02P2 and stratified by testicular radiation. Five-year EFS for B-ALL patients with ITR was 65.0 ± 8.8% (Figure 2A), whereas 5-year OS was 73.1 ± 8.3% (Figure 2B). Five-year EFS was 72.7 ± 14.4% for those who receive testicular radiation and 60.7 ± 11.5% for patients who did not (Figure 2C). In comparison, 5-year OS for patients with ITR treated with testicular radiation was 72.7 ± 14.4% compared to 71.4 ± 10.6% for patients who did not receive testicular radiation (Figure 2D)

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TABLE 1

AALL02P2 protocol design for ITR patients

Treatment	Dosage	Timing
High-dose methotrexate (HDMTX) (week -2)	5 g/m^2 IV over 24 hr with LV rescue	Week –2
Induction (weeks 1–4)		
Dexamethasone (DEX)	10mg/m^2/day PO daily	Weeks 1–4
Vincristine (VCR)	1.5mg/m^2 IV weekly	Weeks 1–4
Daunorubicin (DNR)	25 mg/m^2 IV weekly	Weeks 1–3
ITT (intrathecal triple, methotrexate/hydrocortisone/ cytar abine, MTX/HC/ARA-C)	Age adjusted	Week 1
Consolidation (weeks 5–10)		
Cytarabine (ARA-C)	3,000 mg/m^2 IV every 12 hr × four doses	Weeks 5, 8
PEG-Asparaginase	2,500 IU/m^2 IM	Weeks 5, 8
Testicular radiation		
Biopsy proven testicular leukemia at end of induction	2,400 cGy over 12 fractions	Weeks 5–9
Intensification I (weeks 11–22)		
HDMTX	5 g/m^2 IV over 24 hr with LV rescue	Weeks 11, 14, 17, 20
6-Mercaptopurine (MP)	50 mg/m^2 PO daily days 2–6	Weeks 11, 14, 17, 20
Etoposide (ETOP)	300 mg/m^2 IV	Weeks 12, 14, 17, 21
Cyclophosphamide (CPM)	500 mg/m^2 IV	Weeks 12, 14, 17, 21
ITT	Age adjusted	Weeks 16, 22
Reinduction (weeks 23–26)		
DEX pulses	10mg/m^2/day PO × 7 days	Weeks 23, 25
VCR	1.5mg/m^2 IV weekly	Weeks 23–26
DNR	25mg/m^2 IV weekly	Weeks 23– 25
Intensification II (weeks 27–50)		
ARA-C	3,000 mg/m^2 IV every 12 hr × 4	Weeks 27, 33, 39, 45
PEG-ASP	2,500 IU/M^2 IM	Weeks 27, 33, 39, 45
ITT	Age adjusted	Weeks 30, 42
MTX	5 g/m^2 IV over 24 hr with LV rescue	Weeks 31, 37, 43, 49
MP	50 mg/m^2 PO daily × 5 days	Weeks 31, 37, 43, 49
ETOP	300 mg/m^2 IV	Weeks 32, 38, 44, 50
CPM	500 mg/m^2 IV	Weeks 32, 38, 44, 50
Chemotherapy (weeks 51–54)		
DEX	10mg/m^2/day PO × 7 days	Weeks 51, 53
VCR	1.5mg/m^2 IV weekly	Weeks 51–53
PEG-ASP	2,500 IU/M^2 IM	Weeks 51, 53
Maintenance (weeks 55–74) 10 week cycles × 2		
DEX	10mg/m^2/day PO × 5 days	Weeks 55, 65

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Treatment	Dosage	Timing
MP	75 mg/m^2 PO daily	Weeks 55–60; 65–70
MTX	20 mg/m^2 IM weekly	Weeks 56–60; 66–74
VCR	1.5mg/m^2 IV weekly	Weeks 61–64; 71–74
CPM	300 mg/m^2 IV weekly	Weeks 61–64; 71–74
ITT	Age adjusted	Weeks 55, 65
Maintenance (weeks 75–106) 10 week cycles × 2		
VCR	1.5mg/m^2 IV monthly	Weeks 75, 79, 83, 87, 91, 95, 99, 103
DEX	10mg/m^2/day PO × 5 days monthly	Weeks 75, 70, 83, 87, 91, 95, 99, 103
MP	75 mg/m^2 PO daily	Weeks 75–106
MTX	20 mg/m^2 IM weekly (not given day of ITT)	Weeks 75–106
ITT	Age adjusted (every 12 weeks)	Weeks 75, 87, 99

IV, intravenous; PO, oral; IM, intramuscular.

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TABLE 2

Patient characteristics AALL02P2

Characteristics	Number	%
Patients		
Enrolled	40	
Eligible	40	
Age, years		
At initial diagnosis	4.62 (median); range 0.34–12.82	
At enrollment	8.89 (median); range 4.65–15.17	
NCI risk at diagnosis		
High	9	25
Standard	26	75
Race		
Asian	1	2.5
Black	2	5
White	31	77.5
Unknown	6	15
Ethnicity		
Hispanic	10	25
Non-Hispanic	28	70
Unknown	2	5

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TABLE 3

On study events

		Radiation therapy	
	Total	**No**	**Yes**
Event			
Death	1	1	0
Relapse (6 ITR and 5 BM)	12	9 (6 ITR, 3 BM)	3 (BM)
SMN	1	1	0
No event	26	18	8
Total	40	29	11

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TABLE 4

AALL02P2 grade 3 and 4 toxicities

Type	Number of events	Percentage
Neutropenia	31	77.5
Febrile neutropenia	26	65.0
Thrombocytopenia	15	37.5
Anaphylaxis	7	17.5
Dehydration	6	15.0
Hyperglycemia	5	12.5
Diarrhea	5	12.5
Mucositis	4	10.0
Thrombotic event	2	5.0
Sepsis	1	2.5