Outcomes of Children treated for Relapsed or Refractory Acute Lymphoblastic Leukaemia: A Single Tertiary Care Centre Experience

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Abstract

Background: Acute Lymphoblastic Leukaemia (ALL) , most common malignancy amongst children with front-line treatment considered major success, 20% of children predicted to either relapse or show resistance to treatment with reported dismal outcomes. Aim: To evaluate clinical characteristics of children diagnosed with refractory / relapsed ALL and to determine 3-year overall survival ouctomes. Method: Retrospective review of patients (aged 1 -14 years) diagnosed with ALL during the period January 2002 to December 2018, data extracted for details of baseline characteristics at diagnosis and at relapse . Results: Total of 347 newly diagnosed children with ALL identified, three induction failures and 28 relapses, with total 31 patients a cohort relapse rate of 9% observed. The male-to-female ratio observed is 4.16:1 and mean duration of CR1 was 26 months : 15 (48%) relapsing [?] 18 months,seven (23%) during 18 to 36 months and nine (29%) relapsed $>$ 36 months of IF or CR1.Eighteen patients (62%) had isolated BM relapse, six (20%) patients experience isolated Extra-medullary relapse and five (17%) patients experienced BM with other sites. Three-year Overall Survival (OS) of the cohort was 62.3%, while of those patients who achieved CR post first-salvage therapy 3-year OS of 79.5% observed with a statistically significant difference, p value $<$0.05 comparing to patients who did not achieve remission post first-salvage therapy (3-year OS: 46.4%). The same statistical difference observed in 3-years OS observed comparing duration of remission of CR prior to relapse: [?] 18 months: 33.2%; 18 – 36 months: 66.7% and $>$ 36 months: 87.5%; the same trend continued when comparing 3-years OS based on risk stratification at relapse: LR: 83.3%; IR: 80% and HR: 44.8%. Conclusion: Incidence and outcomes reported on this study is comparable to internationally reported data with duration of CR1, risk-stratification at relapse and remission status post-salvage therapy determined as significant prognostic factors for survival. No survivial difference amongst patients who received HSCT after induction to those who received chemotherapy, could be attributed to a smaller sample size warranting a multi-institutional observational study. The findings corroborates with the need for novel therapies and treatment approaches in these group of patients

Introduction:

Acute Lymphoblastic Leukaemia (ALL), is one of the most common malignancy diagnosed in children and is characterized by diffuse replacement of bone marrow and peripheral blood with neoplastic cells and constitutes for more than a quarter of all pediatric cancers(1, 2). Front-line treatment in ALL is considered a major success and one of the most curable cancers in children with an overall survival rate $>$ 80%, these favourable survival outcomes are attributable to several strategies including combination of chemotherapeutic agents, risk-based stratification and allocation of treatment and prophylactic CNS therapy.(3, 4) Despite substantial improvements in the treatment strategies, approximately 20% of the patients are predicted to relapse and with high incidence of ALL in children, recurrent leukaemia is a relatively common diagnosis being managed by pediatric oncologists(1, 3).

Certain risk-determining factors for relapse have been identified guiding the treating pediatric oncologists

in planning treatment strategies (intensity) and prognosis, factors those have been extensively reported in the literature includes time to relapse from first complete remission (< 36 months from diagnosis) , site of relapse and immunophenotype (B-cell vs. T-cell). Survival amongst relapsed patients is generally predicted by site of relapse and duration of first complete remission, with bone marrow and early relapse reported to be associated with inferior prognosis when compared to isolated extra-medullary or late relapse. Although, clinical remission can be accomplished in majority of relapses, however, long-term survival rates ranges from 40% -50% (5, 6).

Treatment of relapsed patients involves reinduction with conventional agents identical to the one's used at initial diagnosis, and Hematopoietic stem-cell transplantation (HSCT) is widely adapted as consolidation therapy in relapsed ALL patients, however benefit of stem cell tranplant in late or multiple relapses needs to established firmly. Therefore, given the overall suboptimal outcomes with conventional, high-dose therapy involved in treating relapsed or refractory patients warrants new therapeutic agents and strategies (3, 7).

Risk-stratified approach is adapted at our institution when treating pediatric patients with relapse or resistance to first-line therapy and through this study we report outcomes from a single tertiary care centre.

Method and Patients:

This is a retrospective case-controlled study of patients aged 1 to 14 years. who either had relapsed after administration of first-line therapy for ALL or were refractory (resistant) to first-line therapy. The study aims at evaluating clinical characteristics of children diagnosed with refractory / relapsed ALL, determining 3-year overall survival rate in children with refractory / relapsed ALL and to compare risk-stratified groups in determining prognostic factors. Medical records of the patients reviewed and data extracted for details of baseline features at the time of diagnosis and at relapse. Pediatric oncology research database was filtered for diagnostic and outcome details of all patients diagnosed with ALL during the period January 2002 untill December 2018 and the study included newly diagnosed patients with Acute Lymphoblastic Leukaemia (ALL) ,aged 1 to14 years at the time of diagnosis , while patients with Down syndrome, histopathological diagnosis of Acute Myeloid Leukaemia (AML) and Mature B-Cell ALL, underlying diagnosis of Bone Marrow Failure syndromes and records with incomplete data constituted the exclusion criteria on this study.

Study Cohort:

As per the above-mentioned eligibility criteria the study cohort comprised of children newly diagnosed with ALL during the period January 2002 until December 2018 aged 1 to 14 years, either refractory to first-line treatment or experiencing relapse at medullary and / or extra-medullary site. The study cohort included patients who received treatment for relapse during the study defined period i.e. January 2002 to December 2018 at King Faisal Specialist Hospital & Research Centre (KFSH&RC), Jeddah, Saudi Arabia.

The study commenced after obtained regulatory approvals from the Institutional Review Board (IRB) utilizing the IRB-approved study Case Report Form (CRF) to abstract data from paper-based and electronic medical charts of the identified study cohort. Date was collected and managed utilizing the REDCap electronic data capture softed hosted by KFSH&RC, Jeddah. The overall conduct of the study was in compliance in Good Clinical Practice (GCP) guidelines and no personal identifiable information ever collected throughout the conduct of the study, while access to study data restricted to the research team through password-controlled users.

First Line Therapy:

Amongst the thirty-one treatment naïve patients risk-stratified first-line therapy,three of whom were stratified as Low- Risk (LR) precursor B-Cell ALL were treated with CCG1891 protocol prior to 2008, which is a 3-drug induction regimen that involves prednisone, VCR (vincristine) L -asparaginase, PVA and CNS-directed consolidation therapy with and two delayed intensification phases. Ten patients categorised as High-Risk (HR) received chemotherapy-regimen that is based on the CCG 1882 protocols that involves 4-drug induction regimen i.e., prednisone, VCR (vincristine), L -asparaginase, PVDA and daunomycin. Chemotherapy regimen for HR patients involved a more intensive consolidation and a single-delayed phase of intensification and

intensified intrathecal therapy was given to patients who did not receive cranial radiation therapy, and prophylactic cranial radiation therapy was administered to older children (aged > 10 years) without CNS disease , while cranio-spinal radiation was administered in patients with CNS-disease. In the two patients diagnosed and stratified as Very High-Risk (VHR) and T-Cell ALL were treated with St.Jude Total XIII B HR protocol. However, from 2008 onwards the chemotherapy regimens changes were in-line with the risk-stratification that took into account the RUNX1-ETV6 translocation in the Lower Risk (LR) category and additional treatment intensification based on the intensified CCG 1900 series: Five LR patients were treated with CCG1991 chemotherapy regimen , while Six HR patients treated with CCG1961 chemotherapy regimen and Five HR patients were treated with COG 0232 chemotherapy protocol that involved a 4-drug regimen, i.e., Cytarabine, VCR, Daunorubicin, Peg-asparaginase, Prednisolone with prolonged induction therapy administered to patients with M2 or M1 disease status with >1% minimal residual disease. There were three patients diagnosed as T cell ALL and treated with the St. Jude Total XIII B HR regimen.

Risk Stratification at Relapse:

The study adapted Children's Oncology Group (COG) definitions for risk-stratification: LR is defined as late B-ALL marrow relapse, end-block 1 MRD <0.1% and late Isolated Extra-Medullary (IEM) relapse, end-block 1 MRD < 0.1% ; Intermediate Risk (IR) defined as late B-ALL marrow, end-block 1 MRD [?] 0.1% and late IEM, end-block 1 MRD [?] 0.1% and High Risk patients defined as early B-ALL marrow relapse, early IEM relapse and T-Cell All relapse irrespective of timing and site. Late IEM relapse is defined as [?] 18 months from diagnosis, while early IEM is < 18 months from diagnosis and early marrow relapse is defined as < 36 months from diagnosis and late marrow relapse as [?] 36 months from diagnosis.

Second Line Therapy :

Second-line therapeutic strategy was determined through study-defined risk assessment, where in patients who were established to be resistant to the standard 4-drug regimen were reinduced with CCG regimen-A that involved HD-AraC (high dose cytosine arabinoside) with fludarabine or idarubicin in six-patents, while the other six-patients with CR1 duration of 18 months re-induced with the CCG regimen B that involved 4-drug induction regimen of PVDA. Patients treated with regimen-A were consolidated with teniposide / AraC, while patients on regimen-B were treated with HD-ARAC /asparaginase. Post-consolidation maintenance therapy continued for 120 weeks utilizing non-resistant drug pairs in both the regimens in patient who were not planned to undergo Hematopoietic Stem Cell transplantation. All patients were intended to received CNS directed radiation therapy: patients with CNS involvement received cranio-spinal radiation with 2400 cGy to the brain and 1200 cGy to the spine, while patients without CNS - disease at relapse received cranial radiation alone (1800 cGy).

In five-patients, UKALR3 regimen: dexamethasone, vincristine, mitoxantrone, peg-asparaginase and intrathecal methotrexate was administered; FLAG regimen with / or without idarubicin in five-patients; REZ-BFM regimen: dexamethasone, mercaptopurine, methotrexate, AraC and asparaginase in three-patients; St. Jude Total XIII B HR protocol in three-patients; while, two-patients were treated with other salvage protocols (one with ICE and one with COG 0232) and one-patient refused therapy.

Patient stratified as HR at relapse or patients stratified as IR or LR with resistance to first-line of salvage therapy were eligible for allogeneic HSCT, if a suitable donor was available. Amongst the 13 out of the 31 patients underwent HSCT, ten patients were stratified as HR, while three patients were stratified as IR at relapse. The source of donor were fully matched HLA (human leukocyte antigen)- identical siblings for all patients and the conditioning regimen used cyclophosphamide (CY) and Total Body Irradiation (TBI), while prophylaxis for Graft-Versus-Host-Disease (GVHD) included MTX (methotrexate) and CSA (cyclosporine).

Study Endpoints:

Patients were established to be under CR if they had an M1 marrow i.e., <5% blasts by bone marrow aspirate subsequent to second-line salvage induction therapy, without evidence of circulating blasts or extra-medullary disease and peripheral count recovery defined as ANC (absolute neutrophil count) > 0.75 x 10^{9}/L

and Plt (platelet) count > 75 x 10 ^{9}/L. Patients who did not attain a CR subsequent to salvage induction therapy were determined to have induction failure. Successive relapses amongst patients who were in CR were pathologically defined confirmed as M3 marrow i.e., [?] 25 % leukemic blasts or presence of extra-medullary disease. Overall survival duration of the cohort for disease-recurrence was determined from relapse date to date last seen and in case of a deceased patient date of demise was used , while overall survival of cohort for diagnosis was determined form diagnosis date to date last seen or date of demise in case of a deceased patient.

Statistical Analysis:

Data were analysed utilizing the IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, N.Y., USA), for all statistical analysis purposes. Data quality assurance measures were applied for data completeness and accuracy and summary of statistics were obtained and analysed as baseline and demographic characteristics were defined using frequencies and percentages for categorical values and relevant variables were cross-tabulated. While mean, median, range applied for follow-up durations, in years. Survival analysis was performed utilizing Kaplan-Meier method, to calculate 3-year overall survival of the cohort as time from diagnosis date to the date last seen or date of death in case of a deceased patient was used to calculate survival time (in years), the difference between survivals were tested using either the long-rank or Taron-Ware test as applicable, p-value of < 0.05 considered statistically significant.

Results:

Cohort Analysis:

A total of 347 newly-diagnosed children with ALL identified from pediatric oncology research database based on the study-defined inclusion and exclusion criteria. The study cohort comprised of thirty-one children who either relapsed or were resistant to first-line therapy and received salvage therapy , statistical analysis analysis was performed on these patients and their clinical characteristics at diagnosis and at relapse are shown in Table 1.

Three patients experienced induction failures (IF) and 28 relapsed, total of 31 patients with a cohort relapse incidence of 9% (31/347) identified. Overall, 4/28 (14%) relapses occurred on first-line therapy and 24 /28(86%) after completion of therapy. In the patients who relapsed, the CR1 duration ranged from 2.3 to 99 months with a mean of 26 months and median of 2 months. while with 15 (48%) patients relapsed [?] 18 months, while seven (23%) relapsed during 18 to 36 months and nine (29%) patients relapsed > 36 months of IF or CR1.Eighteen patients (62%) had isolated Bone Marrow (BM) relapse, six (20%) patients experienced isolated Extra-medullary relapse (four patients experienced isolated CNS relapse and one-patient experienced isolated testicular relapse) and the remaining five (17%) patients experienced BM with other sites(BM+CNS in four patients and BM + Testis in one patient). Risk stratification of patients at relapse was completed as LR in two (6%) patients, IR in seven (23%) patients and majority of the patients twenty-two (71%) patients were stratified as HR prior to salvage therapy was administered. Seventeen patients (55%) patients first-salvage chemotherapy, while fourteen (45%) received second-salvage therapy and Thirteen (42%) patients proceeded to receive Hematopoietic Stem Cell Transplantation (HSCT). The above-mentioned clinical features of relapsed patient are shown in Table 2.

Survival and Remission status:

Within all relapse sites and categories who received salvage chemotherapy, eleven (36%) patients demonstrated Complete Remission (CR) post-first salvage therapy, while twenty patients (64%) patients went on to receive second-salvage therapy and a remission was achieved in 11/20 patients, thus an overall remission rate of 71% was observed in the study cohort. While, OS of all 31 patients at 3- years from diagnosis was 62.3% with a median follow-up of 3.4 years (range: 0.9 to 13.2 years), while of those patients who atained CR post first-salvage therapy (n=11) an overall survival at 3-years of 79.5% was observed with a statistically significant (p- value <0.05) difference when compared to patients who did not achieve remission post first-salvage therapy (3-year OS: 46.4%). Similarly, a statistically significant (p- value <0.05) difference in

OS at 3-years was observed when comparing duration of remission of CR prior to relapse: [?] 18 months: 33.2%; 18 – 36 months: 66.7% and > 36 months: 87.5% , this difference in survival outcomes found to be statistically significant at p-value < 0.05 . The same trend of statistical significance (p- value <0.05) observed when comparing OS at 3-years based on risk stratification at relapse: LR: 83.3%; IR: 80% and HR: 44.8%. However, when the OS was compared at 3 years for site of relapse no statistical significance observed: Extramedullary relapse (CNS / testis):83.3%; BM: 56.7% and combined sites (B< + CNS / BM + testis): 62.5%. The above-mentioned survival outcomes are summarized in Figure 1 as Kaplan meier curves.

Chemotherapy vs. HSCT

Thirteen patients went on to receive stem cell transplant form fully matched, HLA identical health siblings as donors, while chemotherapy alone was administered in rest of the patients . From the transplanted group of patients all of them achieved full-engraftment, however four patients relapsed, while three patients died in remission due to toxicity related to the transplant and could be characterised as transplant related mortality. Out of the 18 patients who received chemotherapy, four patients have relapsed, while 11 patients died due to treatment – related toxicities. When comparing OS at 3 -years who proceeded to receive HSCT vs. chemotherapy (61.4% vs. 27.3%) no statistical significance was observed as demonstrated in Figure 2

Discussion:

With the current advances in chemotherapy regimens the 5 -year survival rate of newly diagnosed children with ALL has greatly increased over the decades and is now reported at about 90% with a cure rate ranging from 80 - 90% after having received initial treatment, however between 10 – 15% of paediatric patients still experience relapse and have poor outcomes(8-10). Site and time of relapse continues to be reported as the most significant factors in survival after relapse. In this study, we adapt and demonstrate an approach that is based ona risk-stratification when treating children with relapsed or refractory ALL to report our risk-factors and outcomes for survival post – relapse in our cohort of patients.

Relapse rate of 9% was observed in our study , which is comparable to findings reported by several groups and much lower than findings reported by Ali et al. and Nguyen et al. reporting rate of relapse at 24.5% and 20.5% respectively(4, 11, 12). The male-to-female ratio observed in this study is 4.16:1, which is similar to several other studies with a higher relapse rate observed in male than females carrying a poor-prognosis factor(4). Another consistency in the findings with other studies was the higher rate of relapse in high-risk group of patients than low-risk patients (71% vs. 29%).Regarding the relapse site, bone marrow relapse was observed in majority of the cases (61%), which is again similar to several other studies(4).

Amongst the relapsed cases, fifteen patients (64%) patients did not achieve remission and this finding is higher than the reported findings in the literature (4, 12), nevertheless our study too demonstrates early response to re-induction therapy is of prognostic value. The higher failure rate of remission in these patients could be attributed to the relapse site [isolated BM relapse in 12 (60%), BM + CNS relapse in 5 (25%), CNS relapse in 2 (10%) and one-patient (5%) experienced testicular relapse] and based on our assumption that leukemia blast cell were inherently resistant to the therapeutic agents admninistered during the first-line therapy and lack of MRD (minimal residual disease) testing during that time could be a factor attributing to sub-optimal disease response to treatment resulting in poorer outcomes.

Regarding the survival correlation between overall survival between relapse events and survival after diagnosis, response to re-induction was found to be the only strongest predictor of survival in our cohort. Our study adapted a risk-stratification strategy based on the duration of remission after first –line therapy and site of relapse and when OS was performed after disease recurrence a particular good –risk cohort was identified and these finding are comparable to the findings described by Belgaumi et al. With regards to HSCT, no risk group seems to have benefitted and the risk of TRM is worth exploring in this group of patients through a multi-center observational study.

At cut-off for analysis (January 2021), 45% of the children with relapse had passed away while 55% are still alive with a median survival time after relapse to death of 7.5 months, which is similar to findings as

reported by Tuong et al(4), however is shorter than the findings reported by other studies and this could be again due to the lack of MRD testing to evaluate response of second line therapy ,use of protocols and / or therapeutic agents that could have been used and / or upgraded(6).

In conclusion, our study shows majority of the relapse events occurred during the first 18-months from first-remission and bone marrow remains the leading site of relapse. Risk-stratification appears to be effective in identifying "better-risk" category but response to re-induction remained the strongest predictor for survival. Patients treated with HSCT who did not fall in the "better-risk" category continues to demonstrate poor outcomes, although it appears that there is no difference of statistical significance in survival outcomes amongst patients who received HSCT vs. Chemotherapy but this could be attributed to a smaller sample size and therefore a multi-institutional observational study is recommended for a larger cohort of patients as follow-up to this study to compare survival outcome and transplant-related toxicity (infectious and non-infectious).

Additionally, Blinatumomab with MRD testing is a significant treatment advancement for children with relapsed or refractory leukemia (13) and may improve overall survival of relapsed patients and therefore a follow-up study at our institution to compare survival outcomes between the two time frames where in Blinatumomab was introduced is also warranted. Findings from this study too corroborates with the need for Novel therapies and approaches to improve universally-reported dismal outcomes in these group of patients.

Ethical Statement:

Study was approved by the Institutional Review Board (IRB) at King Faisal Specialist Hospital & Research Centre, Jeddah, Saudi Arabia. Informed consenting requirement was waived by the IRB, as the study design is a retrospective chart-review study with no direct interaction with the human subjects. Data collected during the study conduct was de-identified maintaining privacy and confidentiality of human subjects. Additionally, the authors declare that they have no conflict of interest.

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