Original Study

The Dana Farber Consortium Protocol for the Treatment of Adolescents and Young Adults With Acute Lymphoblastic Leukemia: A Single Institution Experience in Saudi Arabia

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Abstract

In this retrospective study we sought to evaluate the feasibility of using the Dana Farber Consortium Protocol in Saudi adolescents and young adult patients with acute lymphoblastic leukemia. The 3-year leukemia-free survival and overall survival rates were 70.2% and 72.5%, respectively. Toxicities included infection, mortality during induction, and pancreatitis, but the incidence and severity of osteonecrosis were less than in Western populations, and no venous thromboembolism was found with the use of enoxaparin prophylaxis.

Background: Recent retrospective analyses and phase II trials have shown differential outcomes in adolescents and young adults when treated with pediatric compared with adult protocols. The aim of this study was to evaluate the efficacy and toxicity of the Dana Farber Consortium Protocol (DFCP) in Saudi young adults diagnosed with de novo acute lymphoblastic leukemia (ALL). **Patients and Methods:** In this retrospective study we included 38 patients with de novo ALL who presented to King Abdulla Medical City in the period from June 2010 to March 2015 and received the DFCP (Princess Margret modified version). **Results:** A total of 38 patients were included with a median age of 19 years. Two patients died during induction treatment, and 35 of 38 patients achieved complete remission (92.1%). With a median follow-up period of 22 months, at 1 and 3 years, leukemia-free survival was 80% and 68%, respectively, and overall survival was 88% and 72%, respectively. Age younger than 21 years showed a significant association with longer survival. Toxicities included febrile neutropenia in all patients during induction, typhilitis in 8/38 (21%), pneumonia in 10/38 (26%), and pancreatitis in 5/38 patients (13%), 3/38 (7.8%) during induction and 2/38 (5.2%) during intensification. Osteonecrosis affected 3/38 patients (7.8%), and was detected during screening in 2/38 (5.2%) of these patients. There were no fractures or surgical interventions, and no venous thromboembolism was recorded. **Conclusion:** Although it might be feasible to use pediatric-inspired protocols in this age group, toxicity cannot be overlooked, and the application of these protocols might require modification of drug doses or schedules relative to those used for younger children. Moreover, additional surveillance and supportive measures should be implemented to maximize benefits while minimizing toxicity.

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Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease that affects all age groups with a pediatric preponderance. Despite improvements in therapy and supportive treatment, the current results of ALL treatment in adults remain dismal, with a survival pattern of 30% to 40% compared with a cure rate exceeding 85% in

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Table 1 The Dana Farber Consortium Protocol

Phase	Description
Induction (4 wk)	Prednisolone 40 mg/m^2 D0 to D28
	Vincristine 1.4 mg/m^2 maximum 2 mg I.V. D0, D7, D14, and D21 (replaced by vinblastine if neurotoxicity)
	Doxorubicin 30 mg/m^2 I.V. D0 and D1 (maximum dose 300 mg/m^2)
	Methotrexate 4 g/m^2 with leucovorin rescue D2 8 to 24 hr after methotrexate
	L-asparaginase (erwina) 25,000 U/m^2 I.M. D4 (not used in Philadelphia-positive cases)
	Intrathecal cytarabine 40 mg D0
	Intrathecal methotrexate (12 mg)/cytarabine (40 mg)/hydrocortisone (15 mg) D14, D28
	Imatinib 600 mg/d D2 to D14 (in Philadelphia-positive cases)
CNS Phase (3 wk)	Vincristine 1.4 mg/m^2 maximum 2 mg I.V. D0
	Doxorubicin 30 mg/m^2 I.V. D0
	6-MP 50 mg/m^2 P.O. D0 to D13
	Intrathecal methotrexate/cytarabine/hydrocortisone D0, D3, D7, D10
	Cranial irradiation 1200 cGY over 8 d if high initial count or CNS disease unless patient will have stem cell transplantation
Intensification (30 wk)	Dexamethasone 9 mg/m^2 P.O. b.i.d. D1 to D5
	6-MP 50 mg/m^2 P.O. D1 to D14
	Vincristine 1.4 mg/m^2 maximum 2 mg I.V. D1
	L-asparaginase 12,500 IU/m^2 I.M. every week
	Intrathecal methotrexate/cytarabine/hydrocortisone at the start of every cycle every 18 wk
	Cycles are repeated every 21 days for 10 cycles. Doxorubicin is replaced with weekly methotrexate starting from cycle 8 to 10 and it is given in the next day after asparaginase at a dose of 30 mg/m^2 P.O. or I.M. weekly. MRI screening for osteonecrosis of hips is done at the end of this phase
Continuation (96 wk)	Dexamethasone 6 mg/m^2 P.O. b.i.d. D1 to D5
	6-MP 50 mg/m^2 P.O. D1 to D14
	Vincristine 1.4 mg/m^2 maximum 2 mg I.V. D1
	Methotrexate 30 mg/mm^2 P.O. or I.M. weekly
	Intrathecal methotrexate/cytarabine/hydrocortisone at the start of every cycle every 18 wk
	During intensification and continuation, changes in the doses of 6-MP and methotrexate were done according to blood count to keep nadir ANC between 500 to 750 $\times$ 10^9/L and platelets 75 to 100 $\times$ 10^9/L. Filgrastim was used for those presenting with ANC $<$500 $\times$ 10^9/L
	Cycles are repeated every 21 d for 24 cycles
	MRI screening for osteonecrosis of hips is done at the end of this phase as well as bone densitometry for osteoporosis

Abbreviations: ANC = absolute neutrophil count; b.i.d. = twice per day; cGY = centiGray; CNS = central nervous system; D = day; I.M. = intramuscular; 6-MP = 6-Mercaptopurine; MRI = magnetic resonance imaging; P.O. = oral.

Table 2 Patient Characteristics

Character	Value (%)
Age, y	
Range	13.5 to 41
Median	19
Sex	
Male, n (%)	25 (65.7)
Female, n (%)	13 (34.2)
Ratio	1.9
WBCs	
Range	1.9 to 396.5 $\times$ 10^9/L
Mean $\pm$ SD	55.6 $\pm$ 93.1 $\times$ 10^9/L
HB	
Range	7.3 to 13.3 g/dL
Mean $\pm$ SD	8.9 $\pm$ 2.3 g/dL
Platelets	
Range	8 to 183 $\times$ 10^9/L
Mean $\pm$ SD	59.7 $\pm$ 47.7 $\times$ 10^9/L
BM Blasts, %	
Range	15 to 99
Mean $\pm$ SD	80.5 $\pm$ 18.3
Immune Phenotype, n (%)	
B cell	32/38 (84.2)
T cell	6/38 (15.7)
CNS Disease at Presentation, n (%)	
Positive	1/38 (2.6)
Negative	37/38 (97.3)
CD20, n (%)	
NA	6/38 (15.7)
Positive	12/38 (31.5)
Negative	20/38 (52.6)
Cytogenetics/FISH, n (%)	
High/very high risk	14/38 (36.8)
Philadelphia-positive	6/14 (42.8)
Complex	3/14 (21.4)
MLL	2/14 (14.2)
Hypodiploid	2/14 (14.2)
Myc	1/14 (7.1)
Others (favorable/intermediate)	24/38 (63.2)
Normal	11/24 (45.8)
IGH rearrangement.	3/24 (12.5)
Hyperdiploid	1/24 (4.2)
Near tetraploid	1/24 (4.2)
t(1,19)	2/24 (8.3)
del p16 (*CDKN2A*) gene	2/24 (8.3)
Triosomy 4	1/24 (4.2)
t(1,14)	1/24 (4.2)
-12p (*ETV6*)	1/24 (4.2)
t(10,14)	1/24 (4.2)

Abbreviations: BM = bone marrow; CNS = central nervous system; FISH = fluorescence in situ hybridization; HB = hemoglobin; IGH = immunoglobulin heavy chain; MLL = mixed-lineage leukemia; Myc = MYC oncogene; WBC = white blood cell.