Published Ahead of Print on December 16, 2013 as 10.1200/JCO.2013.48.6522
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.48.6522

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Intensive Chemotherapy for Childhood Acute Lymphoblastic Leukemia: Results of the Randomized Intercontinental Trial ALL IC-BFM 2002

Jan Stary, Martin Zimmermann, Myriam Campbell, Luis Castillo, Eduardo Dibar, Svetlana Donska, Alejandro Gonzalez, Shai Izraeli, Dragana Janic, Janez Jazbec, Josip Konja, Emilia Kaiserova, Jerzy Kowalczyk, Gabor Kovacs, Chi-Kong Li, Edina Magyarosy, Alexander Popa, Batia Stark, Yahia Jabali, Jan Trka, Ondrej Hrusak, Hansjörg Riehm, Giuseppe Masera, and Martin Schrappe

See accompanying editorial doi: 10.1200/JCO.2013.53.2754

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on December 16, 2013.

Written on behalf of the International Berlin-Frankfurt-Münster Study Group.

Supported by Grant No. 00064203 from the Ministry of Health, Czech Republic for Conceptual Development of Research Organization (University Hospital Motol, Prague, Czech Republic).

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00764907.

Corresponding author: Jan Stary, MD, Department of Pediatric Hematology/Oncology, Charles University and University Hospital Motol, V Uvalu 84, CZ-150 06, Prague 5, Czech Republic; e-mail: jan.stary@lfmotol.cuni.cz.

0732-183X/13/3199-1/$20.00

DOI: 10.1200/JCO.2013.48.6522

ABSTRACT

Purpose
From 2002 to 2007, the International Berlin-Frankfurt-Münster Study Group conducted a prospective randomized clinical trial (ALL IC-BFM 2002) for the management of childhood acute lymphoblastic leukemia (ALL) in 15 countries on three continents. The aim of this trial was to explore the impact of differential delayed intensification (DI) on outcome in all risk groups.

Patients and Methods
For this trial, 5,060 eligible patients were divided into three risk groups according to age, WBC, early treatment response, and unfavorable genetic aberrations. DI was randomized as follows: standard risk (SR), two 4-week intensive elements (protocol III) versus one 7-week protocol II; intermediate risk (IR), protocol III × 3 versus protocol II × 1; high risk (HR), protocol III × 3 versus either protocol II × 2 (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP] option), or 3 HR blocks plus single protocol II (Berlin-Frankfurt-Münster [BFM] option).

Results
At 5 years, the probabilities of event-free survival and survival were 74% (± 1%) and 82% (± 1%) for all 5,060 eligible patients, 81% and 90% for the SR (n = 1,564), 75% and 83% for the IR (n = 2,650), and 55% and 62% for the HR (n = 846) groups, respectively. No improvement was accomplished by more intense and/or prolonged DI.

Conclusion
The ALL IC-BFM 2002 trial is a good example of international collaboration in pediatric oncology. A wide platform of countries able to run randomized studies in ALL has been established. Although the alternative DI did not improve outcome compared with standard treatment and the overall results are worse than those achieved by longer established leukemia groups, the national results have generally improved.

J Clin Oncol 31. © 2013 by American Society of Clinical Oncology

INTRODUCTION

The International Berlin-Frankfurt-Münster Study Group (I-BFM-SG) comprises national study groups from more than 30 countries worldwide that collaborate in working committees to address important aspects of clinical and basic research in pediatric leukemia and lymphoma. Over the last 20 years, the BFM group conducted several highly successful clinical trials for childhood acute lymphoblastic leukemia (ALL) by using chemotherapy schedules based on the original BFM backbone.[1] Modifications of essentially all elements of therapy have been evaluated in randomized trials conducted by the most experienced European cooperative groups.[1-3] The progressive broadening of the I-BFM-SG to include new national groups with limited resources and less experience with complex and intensive chemotherapy regimens dictated the need for a study tailored to local conditions. On the basis of the pioneering findings of the BFM group on measurement of early response to therapy (ie, prednisone response [PR] in peripheral blood on day 8, and percentage of bone marrow [BM] blasts on day 15), all patients could be stratified in risk groups by widely accessible methods.[4,5]

Recently, many study groups have shown that polymerase chain reaction (PCR) quantification of