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Long-Term Follow-Up of the Imatinib GRAAPH-2003 Study in Newly Diagnosed Patients with De Novo Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A GRAALL Study

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A B S T R A C T

We report here the results of the GRAAPH-2003 trial with long-term follow-up in 45 patients with de novo Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). Imatinib-based strategy improved the 4-year overall survival (OS) up to 52% versus 20% in the pre-imatinib LALA-94 trial ($P = .0001$). Despite the selection in patients who actually underwent transplantation, these results suggest that allogeneic or autologous stem cell transplants (SCTs) still have a place in overcoming the poor prognosis of Ph+ ALL in the era of imatinib therapy. OS was 50% after allogeneic SCT (24 patients), 33% in patients without a transplantation (9 patients), and 80% after autologous SCT (10 patients without allogeneic donor or >55 years, including 7 patients in complete molecular response).

INTRODUCTION

Philadelphia chromosome positive (Ph+) is the most frequent recurrent cytogenetic abnormality observed in adult patients diagnosed with acute lymphoblastic leukemia (ALL). Before the tyrosine kinase inhibitor (TKI) era, the outcome of patients with Ph+ ALL was very poor, with long-term survival rates, at best, reaching 20% in most studies [1,2]. Allogeneic stem cell transplant (SCT) has been considered as the consolidation treatment of choice once achieving a first complete remission (CR), as it provides the best outcome in this setting [3]. In recent years, the most significant advance in term of treatment has been the introduction of TKIs into Ph+ ALL treatment protocols. Several groups have shown that the combination of concurrent or alternating use of imatinib with high-dose chemotherapy has significantly improved the outcome of adults and children with newly diagnosed Ph+ ALL, with higher CR rates (nearly 95%) and 12-month overall survival (OS) reaching approximately 75% [4-9]. However, to date, there is no evidence that TKIs may impact on the long-term outcome of patients with Ph+ ALL, because the follow-up of published studies did not exceed 2 years [4-10]. In a first analysis of the GRAAPH-2003 study, CR rate, 18-month disease-free survival (DFS), and OS were 96%, 51%, and 65%, respectively [11]. In the present analysis, results of the GRAAPH-2003 study have been actualized with a longer median follow-up reaching 3.86 years.

PATIENTS AND METHODS

From January 2004 to October 2005, 45 patients with newly diagnosed de novo Ph+ ALL (median age, 45 years; range, 16-59 years) were included in the GRAAPH-2003 study. The Ph+ was detected by standard karyotype and/or fluorescence in situ hybridization analysis and/or *BCR-ABL* fusion transcript detection by reverse transcription-PCR. Patients with previous chronic myeloid leukemia or myeloproliferative disorders were excluded. All patients gave their written informed consent before the study. The study was approved in March 2003 by the institutional review board of Hôpital Purpan, Toulouse, France, and conducted in accordance with the Declaration of Helsinki. Details regarding this study have been published elsewhere [11].

The protocol schedule is summarized in Figure 1. Following a 7-day prednisone pre-phase, corticosteroid sensitivity (CS) was assessed by peripheral blood examination and was defined as $<1.0 \times 10^9$/L residual circulating blasts. Chemotherapy sensitivity (ChS) was assessed by peripheral blood and bone marrow (BM) examination 8 days after the start of an induction chemotherapy including daunorubicin, cyclophosphamide,

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GRAPH-2003: induction and consolidation therapy

	Dose	Time, d
Prephase		
Prednisone	60 mg/m²/d PO	Between −7 and −1
Methotrexate	15 mg IT	Between −7 and −4
Standard induction, wks 1-2		
Daunorubicin	50 mg/m²/d IV	1 to 3
Cyclophosphamide	750 mg/m²/d IV	1
Vincristine	2 mg IV	1, 8
Prednisone	60 mg/m²/d PO	1 to 14
L-asparaginase	6000 IU/m²/d IV	8, 10, 12
Triple IT	—‡	1, 8
Standard induction, wks 3-4		
Daunorubicin	30 mg/m²/d IV	15 to 16
Cyclophosphamide	750 mg/m²/d IV	15
Vincristine	2 mg IV	15, 22
L-asparaginase	6000 IU/m²/d IV	20, 22, 24, 26, 28
G-CSF lenograstim	150 μg/m²/d SC or IV	From 17
DIV combination*		
Vincristine	2 mg IV	1, 8, 15, 22
Dexamethasone	40 mg PO or IV	1-2, 8-9, 15-16, 22-23
Imatinib	800 mg/d PO	1 until SCT
Triple IT	—‡	1, 8, 15, 22
HAMI combination†		
Mitoxantrone	10 mg/m²/d, IV	1 to 3
Cytarabine	2000 mg/m²/12h, IV	1 to 4
Imatinib	600 mg/d PO	1 until SCT
Triple IT	—‡	8, 15
G-CSF filgrastim	5 μg/kg/d SC or IV	From 9

PO indicates per os (orally); IT, intrathecally; IV, intravenously; SC, subcutaneously.

*Administered at day 15 of the standard induction course in patients with corticoresistant and/or chemoresistant ALL.

†Administered after hematologic CR achievement as consolidation in patients with corticosensitive and chemosensitive ALL.

‡Consisted of 15 mg methotrexate, 40 mg cytarabine, and 40 mg dexamethasone, all administered intrathecally.

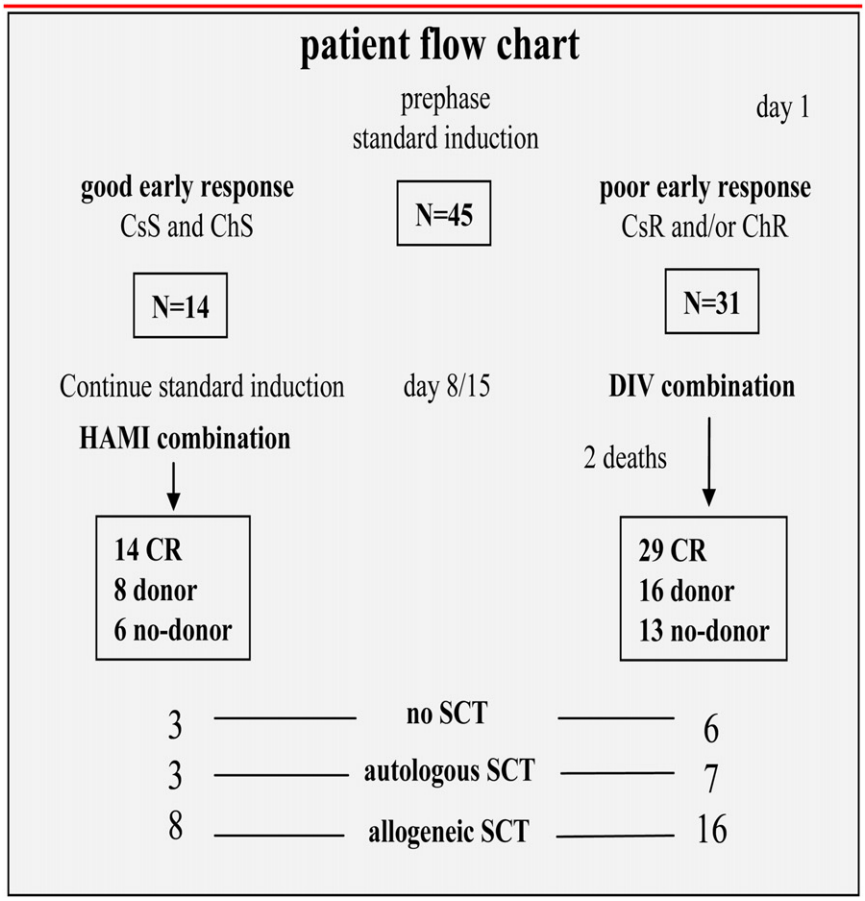

Figure 1. Treatment and patient flow chart.