A multicenter total therapy strategy for *de novo* adult Philadelphia chromosome positive acute lymphoblastic leukemia patients: final results of the GIMEMA LAL1509 protocol

Sabina Chiaretti,[1] Michela Ansuinelli,[1] Antonella Vitale,[1] Loredana Elia,[1] Mabel Matarazzo,[1] Alfonso Piciocchi,[2] Paola Fazi,[2] Francesco Di Raimondo,[3] Lidia Santoro,[4] Francesco Fabbiano,[5] Catello Califano,[6] Giovanni Martinelli,[7] Francesca Ronco,[8] Felicetto Ferrara,[9] Nicola Cascavilla,[10] Catia Bigazzi,[11] Alessandra Tedeschi,[12] Simona Sica,[13,14] Nicola Di Renzo,[15] Angela Melpignano,[16] Germana Beltrami,[17] Marco Vignetti[2] and Robin Foà[1]

[1]Section of Hematology, Department of Translational and Precision Medicine, Sapienza University, Rome; [2]GIMEMA Data Center, Fondazione GIMEMA, Rome; [3]Section of Hematology, Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania; [4]Struttura Complessa di Ematologia e Trapianto Emopoietico-A.O. S.G.Moscati, Avellino; [5]Division of Hematology and Bone Marrow Transplantation, Ospedali Riuniti Villa Sofia-Cervello, Palermo; [6]Onco-Ematologia Ospedale Pagani, Salerno; [7]Seragnoli Institute of Hematology, Bologna University School of Medicine, Bologna; [8]Operative Unit of Hematology, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria; [9]Division of Hematology and Stem Cell Transplantation Program, AORN Cardarelli Hospital, Naples; [10]Casa Sollievo della Sofferenza IRCCS, San Giovanni Rotondo; [11]Department of Hematology and Stem Cell Transplantation Unit, C.G. Mazzoni Hospital, Ascoli Piceno; [12]ASST Grande Ospedale Metropolitano Niguarda, Milan; [13]Fondazione Policlinico Universitario A. Gemelli, Rome; [14]Università Cattolica del Sacro Cuore, Rome; [15]Department of Hematology and Stem Cell Transplant, Presidio Ospedaliero Vito Fazzi, Lecce; [16]A. Perrino Hospital, Brindisi and [17]Policlinico San Martino, Genoa, Italy

 doi:10.3324/haematol.2020.260935

Received: May 29, 2020.

Accepted: December 24, 2020.

Pre-published: February 4, 2021.

Correspondence: *SABINA CHIARETTI* - chiaretti@bce.uniroma1.it

ROBIN FOÀ - rfoa@bce.uniroma1.it

Supplemental Materials and Methods

CNS prophylaxis

CNS prophylaxis was mandatory: 5 medicated rachicenteses (intrathecal methotrexate, 12 mg, and intrathecal methylprednisolone, 20 mg) were carried out during induction (at diagnosis, day +22, +45, +57 and 85) and then every month for a total number of 12.

MRD monitoring after induction

For MRD monitoring, *BCR-ABL1* levels were normalized to the number of the *ABL1* control gene and expressed as *BCR-ABL1*/*ABL1*×100; the level of *BCR-ABL1* expression was then converted into a base 10 logarithmic scale. In determining the integrity of RNA, the criteria for excluding RNA samples was established as an ABL1 copy numbers <10000 for negative samples and <1000 for those positive and quantifiable. The number of BCR/ABL1 copies was normalised with respect to the number of ABL1 copies and expressed as the number of BCR-ABL1/ABL1 copies x 102.

After the induction phase, MRD was monitored every two months during the first 6 months for patients who received dasatinib only and every three months during the subsequent 6 months, then every four months during the second and third year, and every six months during the fourth and fifth year. For patients who underwent an allo-SCT, molecular testing was carried out every two months during the first year, then every four months during the second and third year and every six months during the fourth and fifth year. For patients who underwent chemotherapy with clofarabine-cyclophosphamide, MRD levels were tested after the first and second cycle, then every two months during the first year, then every four months during the second and third year and every six months during the fourth and fifth year.

Supplemental Table 1. Number and type of adverse events occurring during protocol

Type of disorder	Overall	Dasatinib induction	Dasatinib consolidation	Clopharabine-Endoxan	Dasatinib after Clopharabine-Endoxan	Allo-SCT	Dasatinib after allo-SCT
Hematological	124 (66%)	62	-	36	-	21	5
Gastrointestinal	12 (6%)	2	-	2	1	6	1
Hepato-biliary	3 (1.5%)	-	-	-	-	2	1
General	7 (3.7%)	-	-	1	-	6	-
Immune	2 (1%)	-	-	-	-	2	-
Infections	12 (6%)	2	-	3	-	7	-
Metabolic	1 (0.5%)	1	-	-	-	-	-
CNS	1 (0.5%)	1	-	-	-	-	-
Laboratory	18 (9.6%)	12	-	1	-	5	-
Renal/Urinary	2 (1%)	-	1	-	-	1	-
Respiratory	2 (1%)	-	-	-	-	2	-
Skin	4 (2.1%)	1	-	-	-	3	-

Additional supplemental figure. For revisors only. DFS according to MRD cut-off level of 10-3