Study Title:	**Allogeneic haematopoietic stem cell transplantation from a matched donor in patients with chronic myeloid leukemia failing to gain normal hemopoiesis under TKLs therapy.**
PI	Carlo Gambacorti Passerini MD Director, Clinical Research Unit S.Gerardo Hospital Via Cadore 48 Monza-Italy Fabio Ciceri MD San Raffaele Scientific Institute Dept of Hematology/Transplant Unit I-20132 Milan
Project-No:	AlloCML
EUDRACT NUMBER	2014-003126-40

1. Introduction

CML is a malignant clonal disorder of hematopoietic stem cells that results in increases in not only myeloid cells but also erythroid cells and platelets in peripheral blood and marked myeloid hyperplasia in the bone marrow. Patients presented typical symptoms as fatigue, anorexia, and weight loss, but about 40 percent of patients are asymptomatic, and in these patients, the diagnosis is based on an abnormal blood count. During the physical examination the most common abnormality is splenomegaly, which is present in up to half of patients [1]

The diagnosis of CML is usually based on detection of the Philadelphia (Ph) chromosome described as a t(9;22) translocation; this abnormality, is present in 95 percent of patients. The remaining 5% shown a variant translocations involving additional chromosomes that have the fusion of the BCR (breakpoint cluster region) gene on chromosome 22 to the ABL (Ableson leukemia virus) gene on chromosome 9. The CML is a stem-cell disease because the Ph chromosome is found in cells from the myeloid, erythroid, megakaryocytic, and B lymphoid lineages. Mutations or deletions of tumor-suppressor genes such as p164 and p53 occur with variable frequency and presumably contribute to the malignant phenotype [2].

The molecular consequence of the t(9;22) translocation is the creation of the fusion protein BCR– ABL, which is a constitutively active cytoplasmic tyrosine kinase.

Bosutinib (SKI-606, Bosulif®; Pfizer, New York, NY, USA) acts as a dual inhibitor of Src and ABL kinases. Compared with other second-generation tyrosine kinase inhibitors (TKIs) only low concentrations of bosutinib are required to ablate BCR-ABL phosphorylation when compared with the first-generation TKI Imatinib (Glivec®, Novartis, Basel, Switzerland). Bosutinib is a potent second-generation inhibitor of chronic myeloid leukemia (CML) cell proliferation in vitro and has been found to be capable of overcoming the majority of imatinib-resistant BCR-ABL mutations [3].

Bosutinib received US FDA and EU European Medicines Agency approval on September 4, 2012 and 27 March, 2013 for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia with resistance or intolerance to prior therapy.

Patients recently diagnosed undergo treatment with TK-inhibitors; a possible cause is represented by the insufficient recovery of normal Ph-hematopoiesis during the treatment. This event is rare but happens in a proportion of 4-5% of CML patients.

The hypothesis of this study is to circumvent this condition by providing a normal hematopoiesis from a HLA- matched donor. While the TKI will be used to control the growth of leukemic cells, the transplant procedure is used to sustain hematopoiesis.

The transplant procedure planned in this study is build on all available evidences to provide the lowest incidence of acute and chronic GvHD.

The use of Tkls transplant carries the risk of inhibiting the newly transplanted hematopoietic cells, as kit, an important kinase in normal bone marrow cells, is frequently blocked by Abl inhibitors. The lack of kit inhibition justify the use of Bosutinib as post-transplant therapy and which could allow a minimal inhibitory activity against the transplanted normal bone marrow.

2. Study design, objectives, endpoints and inclusion criteria

This is a prospective, multi-center, non-randomized, no profit, open label phase II trial in which the primary objective is the evaluation of complete cytogenetic responses at 12 months based on at least 20 mataphases, while efficacy, safety and quality of life (QoL) are the secondary objectives of the study.

Two patients have been enrolled with inclusion criteria of CML (CP) failing to gain normal hemopoiesis under TKLs therapy with a bone marrow match donor.

The first visit for the first patient was 29/09/2017 and the first visit for the last patient was 03/10/2017.

During the treatment two SAE have been notified by Investigators: acute hepatitis grade 3 and untreatable vomiting grade 3; in both cases the drug was not considered related whit the event. Bosutinb was related instead with an adverse events: persisting vomiting and diarrhea.

There are no data available because patients have not completed the study: 1 is off study due to Investigator's decision and 1 patient exit on the 08/11/2018 from the study due to intolerance due to bosutinib.

The study was completed in all stages on the 29/09/2018.

ASST MONZA OSPEDALE SAN GERARDO
U.O. Ematologia
Prof. GAMBACORTI CARLO
Matricola N. 97975
C. F. GMB CRL 57M26 F205W

Bibliography

[1] Chronic myeloid leukemia ;The New England Journal of Medicine; CHARLES L. SAWYERS, M.D. April 29, 1999

[2] The spectrum of molecular alterations in the evolution of chronic myelocytic leukemia. Ahuja H, Bar-Eli M, Arlin Z, et al. J Clin Invest 1991; 87:2042-7.

[3] In vitro and in vivo activity of SKI-606, a novel Src-Abl inhibitor, against imatinib-resistant Bcr-Abl+ neoplastic cells. Puttini M, Coluccia AM, Boschelli F, et al..Cancer Res.2006;66(23):11314–11322.