Myeloablative, reduced toxicity versus standard conditioning in AML: a randomized clinical trial from Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

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Myeloablative, reduced toxicity versus standard conditioning in AML: a randomized clinical trial from Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

Anna Grassi[* 1], Caterina Micò[1], Elena Oldani[2], Cristina Boschini[2], Alessandro Busca[3], Bruno Benedetto[3], Irene Cavattoni[4], Stella Santarone[5], Roberto Raimondi[6], Mauro Montanari[7], Giuseppe Milone[8], Patrizia Chiusolo[9], Giorgina Specchia[10], Stefano Guidi[11], Francesca Patriarca[12], Andrea Bacigalupo[13], Antonio M. Risitano[14], Giorgia Saporiti[15], Massimo Pini[16], Entico Maria Pogliani[17], William Arcese[18], Giuseppe Marotta[19], Angelo Michele Carella[20], Arnon Nagler[21], Paolo Corradini[22], Domenico Russo[23], Emilio Paolo Alessandrino[24], Giovanni Fernando Torelli[25], Nicola Mordini[26], Rosanna Scimè[27], Alberto Bosi[28], Arianna Masciulli[29], Rosa Maria Marfisi[30], Alessandro Rambaldi[1]

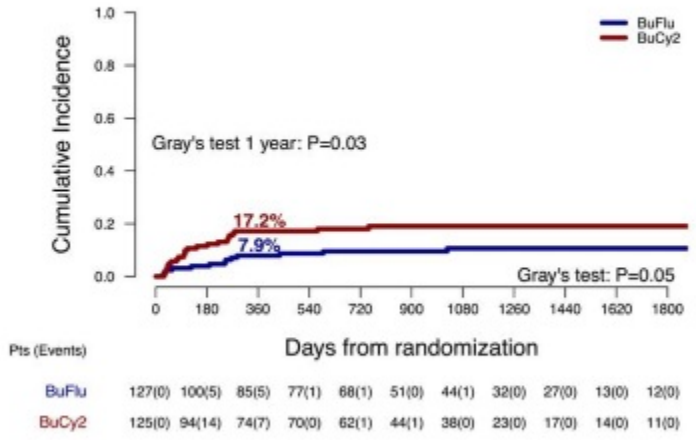
[1]Hematology and BMT Unit, AZIENDA OSPEDALIERA PAPA GIOVANNI XXIII, [2]Hematology and BMT Unit, Ospedale Papa Giovanni XXIII, Bergamo, [3]Bone Marrow Transplantation Unit, azienda ospedaliera-universitaria città della salute, Torino, [4]Bone Marrow Transplantation Unit, Ospedale Civile Hematology and Bone Marrow Transplant Unit, Bolzano, [5] Bone Marrow Transplantation Unit, Ospedale Civile BMT Center Pescara, Pescara, [6]Hematology and Bone Marrow Transplant Unit, Ospedale San Bortolo, Vicenza, [7]Hematology, Azienda Ospedali Riuniti, Ancona, [8]Hematology and BMT Unit, Ospedale Ferrarotto, Catania, [9]Division of Hematology, Policlinico A. Gemelli, Roma, [10]Department of Emergency and Organ Transplantation, Section of Hematology with Transplantation, Medical School, University of Bari, Bari, [11] Department of Hematology, BMT Unit, AOU Careggi, University of Firenze, Firenze, [12]Hematology and Bone Marrow Transplant Unit, Azienda Ospedaliera -Universitaria , Udine, [13]Hematology and Oncology Department, IRCCS AOU San Martino - IST, Genova, [14]Hematology, Federico II University of Naples, Napoli, [15]Hematology - BMT Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milano, [16]Hematology, AO SS. Antonio e Biagio e C. Arrigo, Alessandria, [17]Hematology and BMT Unit, Ospedale San Gerardo, University of Milano Bicocca, Monza, [18] Hematology Division - Stem Cell Transplant Unit, University of Rome Tor Vergata, Roma, [19]Hematology, Azienda Ospedaliera Universitaria Senese, Siena, [20]Hematoloy-BMT Unit, IRCCS, Casa sollievo della sofferenza, San Giovanni Rotondo (Fg), Italy, [21]Hematology and BMT Unit, Chaim Sheba Medical Center, Tel Hashomer,, Israel, [22]Hematology-Bone Marrow Transplantation Unit, Fondazione IRCCS Istituto Nazionale Tumori and University of Milano, Milano, [23]BMT Unit, Spedali Civili , Brescia, [24]BMT Unit, IRCCS Fondazione Policlinico San Matteo & University , Pavia, [25]Cellular Biotechnologies & Hematology, Sapienza University, Roma, [26]Hematology, Azienda Ospedaliera S. Croce e Carle, Cuneo, [27]Hematology and BMT Unit, Ospedali Riuniti Villa Sofia-Cervello,, Palermo, [28]Hematology and BMT Unit, AOU Careggi, University of Firenze, Firenze, [29]Fondazione Mario Negri Sud, Santa Maria Imbaro , [30]Fondazione Mario Negri Sud, S. Maria Imbaro, Italy

Preferred Method of Presentation: Oral Presentation

Introduction: The combination of a myeloablative dose of intravenous (iv) busulfan with cyclophosphamide (BuCy2) is the standard conditioning regimen for allogeneic hematopoietic stem cell transplantation in AML. In patients older than 40 years, it can be associated to high non relapse mortality (NRM). The same myeloablative dose of busulfan combined to fludarabine (BuFlu) may be associated to a lower NRM

Materials (or patients) and methods: The standard conditioning with iv busulfan at a dose of 0.8 mg/kg/6h for 4 consecutive days for a total dose of 12.8 mg/kg, in combination with cyclophosphamide at the dose of 60 mg/kg/day for 2 consecutive days for a total dose of 120 mg/kg (BUCY2 arm) was randomly compared to the same dose of busulfan combined with fludarabine at the dose of 40 mg/m^2/day for 4 consecutive days, for a total dose of 160 mg/m2(BUFLU arm). Eligible were patients with a diagnosis of AML in 1st or 2nd complete remission (CR) with an age ≥40 and ≤ 65 years, and the availability of an HLA compatible sibling or unrelated donor. The GvHD prophylaxis was based on

conventional Cyclosporine A and Methotrexate. In case of unrelated donors, ATG was given at a total dose of 5 mg/kg. The primary study end-point was the one-year NRM using an intent-to-treat analysis.
Results: 252 patients were assessed for eligibility: 125 were randomized to BuCy2 (121 received the allocated intervention, 3 withdrew consent and 1 relapsed before conditioning) while 127 were randomized to BuFlu (124 received the allocated intervention and 3 relapsed before conditioning).Patients were stratified according to donor type and remission (1st vs. 2nd or more). The main clinical and transplant characteristics were well balanced between the randomization arms. The median age was 51 years, 85% of patients was in 1st remission and the ELN risk subgroups were good (11%), intermediate-1 (49%), intermediate-2 (16%) and adverse (25%). The donor was a sibling related (45%) or matched unrelated (55%) while the stem cell graft was the peripheral blood in the majority of cases. On an intent to treat basis, at 1 year, the NRM in the BUCY2 arm was 17.2% vs. 7.9% in the BUFLU (Gray Test P=0.03). At 2 years and throughout the study, the same significantly different NRM was observed between study arms being respectively 18.2% vs. 8.9% and 19% vs. 9.7% (Gray Test P=0.05) (Figure 1). By forest plots analysis the experimental treatment was better in all strata and particularly in patients in CR1. A non-significant lower incidence of relapse was documented in the BUCY2 vs. the BUFLU arm being 22.1% vs. 25.2% at 1 year, respectively (Gray test 0.47) and no difference could be detected by forest plot analysis in any strata. At 4 year, in the BuFlu and the BuCy2 arm respectively, the leukemia free survival was 51% vs. 42% and the overall survival 55% vs. 54%. The overall (grade II-IV) cumulative incidence of acute GVHD was slightly higher in the BuCy2 arm and this difference was significant (p= 0.0083) when only grade III and IV were considered.
Image / Graph:



Conclusion: The conditioning regimen based on Busulfan and Fludarabine was associated with a lower non-relapse mortality and less acute GvHD (grade III-IV), with a similar incidence of relapse and comparable LFS and OS. This myeloablative, albeit reduced toxicity program is a valid alternative for older AML patients.

Disclosure of Interest: A. Grassi Conflict with: Pierre Fabre, Pharma, C. Micò: None Declared, E. Oldani: None Declared, C. Boschini: None Declared, A. Busca: None Declared, B. Benedetto: None Declared, I. Cavattoni: None Declared, S. Santarone: None Declared, R. Raimondi: None Declared, M. Montanari: None Declared, G. Milone: None Declared, P. Chiusolo: None Declared, G. Specchia: None Declared, S. Guidi: None Declared, F. Patriarca: None Declared, A.

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