Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial

Riccardo Bruna,[1§] Fabio Benedetti,[2] Carola Boccomini,[3] Caterina Patti,[4] Anna Maria Barbui,[5] Alessandro Pulsoni,[6] Maurizio Musso,[7] Anna Marina Liberati,[8] Guido Gini,[9] Claudia Castellino,[10] Fausto Rossini,[11] Fabio Ciceri,[12] Delia Rota-Scalabrini,[13] Caterina Stelitano,[14] Francesco Di Raimondo,[15] Alessandra Tucci,[16] Liliana Devizzi,[17] Valerio Zoli,[18] Francesco Zallio,[19] Franco Narni,[20] Alessandra Dondi,[21] Guido Parvis,[22^] Gianpietro Semenzato,[23] Francesco Lanza,[24°] Tommasina Perrone,[25] Francesco Angrilli,[26] Atto Billio,[27] Angela Gueli,[1] Barbara Mantoan,[28] Alessandro Rambaldi,[5,29] Alessandro Massimo Gianni,[1] Paolo Corradini,[17,29] Roberto Passera,[30] Marco Ladetto,[19] Corrado Tarella[*1,31]

[1]Onco-Hematology Division, IEO, European Institute of Oncology IRCCS, Milano; [2]Hematology University Division, Verona; [3]Hematology Division, Città della Salute Hospital, Torino; [4]Hematology Division, Azienda Villa Sofia-Cervello, Palermo; [5]Hematology Division, Papa Giovanni XXIII Hospital, Bergamo; [6]Department of Cellular Biotechnologies and Hematology, La Sapienza University, Roma; [7]Hematology Unit, La Maddalena Hospital, Palermo; [8]SC Oncoematologia, Università degli Studi di Perugia; [9]Hematology University Division, Ancona; [10]Department of Hematology, S. Croce e Carle Hospital, Cuneo; [11]Hematology University Division, Monza; [12]Hematology Unit HSR, Milano; [13]Oncologia Medica, Cancer Institute FPO, IRCCS, Candiolo; [14]Hematology Division, Reggio Calabria; [15]Hematology Univiversity Division, Catania; [16]Division of Hematology, Brescia; [17]University Division of Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; [18]Hematology Division, S. Camillo Hospital, Roma; [19]SC Ematologia AO SS Antonio e Biagio e Cesare Arrigo, Alessandria; [20]Hematology University Division, Modena; [21]Division of Oncology, Modena; [22]Division of Internal Medicine, S. Luigi Hospital, Orbassano; [23]Hematology University Division, Padova; [24]Hematology Unit, Cremona; [25]Hematology University Division, Bari; [26]Hematology Division, Pescara; [27]Hematology Division, Bolzano; [28]Hematology University Division, Città della Salute Hospital, Torino; [29]Department of Oncology and Onco-Hematology, University of Milan, Milano; [30]Nuclear Medicine Division, Città della Salute Hospital, Torino and [31]Department of Health Sciences, University of Milan, Milano, Italy

Present address: [§]Division of Hematology, Ospedale Maggiore della Carità, Novara, ^University Hematology Division, Mauriziano Hospital, Torino °Hematology and SCT Unit, Ospedale di Ravenna

 doi:10.3324/haematol.2018.209932

Received: October 22, 2018.

Accepted: April 10, 2019.

Pre-published: April 11, 2019.

Correspondence: *CORRADO TARELLA* - corrado.tarella@unimi.it

METHODS: ADDITIONAL DETAILS

Patient characteristics

Between March 2000 and May 2005, a total of 136 patients were enrolled in the multicenter randomized study, launched in Italy among centers affiliated with GITMO (Gruppo Italiano Trapianto Midollo Osseo) and/or to the Italian Lymphoma Intergroup known as IIL (now incorporated into FIL, Fondazione Italiana Linfomi) [9]. All recruiting Centers were qualified by GITMO to perform autologous stem cell transplantation. The study was specifically designed for the first-line treatment of patients with a histologically proven diagnosis of FL according to the Revised European-American Lymphoma/World Health Organization (REAL/WHO) lymphoma classification (grades I, II, and III; patients with grade IIIb were not excluded) [14]. Patients aged 16 to 60 years were eligible if they had Ann Arbor stage III or IV and a high-risk prognostic presentation, according to the prognostic risk scores in use at the time the protocol was designed, i.e. the age-adjusted IPI score (score of 2 or greater) and the IIL score for FL (score 3 or greater) [15, 16]. As detailed in the CONSORT Diagram (online Supplement), 136 patients entered the study protocol; two patients in the CHOP-R arm were then excluded from the analysis: one patient withdrew the consent and one lacked a documented high-risk score. Main features of the 134 evaluable patients and of patients who are presently alive vs. those who have died since protocol entrance are reported in Table 1 in the text.

Study design and treatment schedule and end-points

The study aim was to assess the superiority of an intensive chemo-immunotherapy strategy including autologous hematopoietic stem cell transplantation (auto-HSCT) compared to conventional chemo-immunotherapy. Thus, following verification of eligibility criteria, a centralized computer generated a simple randomization sequence and patients were randomly assigned either to the intensified or conventional arm.

Briefly, the conventional arm consisted of six courses of CHOP chemotherapy,

followed by infusions of four weekly doses of 375 mg/m2 rituximab. The efficacy and feasibility of the sequential CHOP-R schedule for FL has been described by Rambaldi et al [17]. The intensified arm included the HDS schedule originally described for low-grade lymphoma, then supplemented with four doses of 375 mg/m2 rituximab (R-HDS) [18-19]. The R-HDS schedule consisted of three phases: (1) intensive debulking; (2) high-dose (HD) chemotherapy with stem cell collection of in vivo purged peripheral blood stem cells; and (3) auto-HSCT, as described previously [9, 18-19]. Two additional rituximab doses were planned in both arms (13 CHOP-R and 7 R-HDS patients) in case of partial remission (PR) or PCR positivity at the end of treatment. Moreover, consolidation radiotherapy was delivered to 31 (47%) CHOP-R and 28 (41%) R-HDS patients. The primary endpoint of the study was event-free survival (EFS), defined according to the 1999 Cheson criteria in use at that time, as detailed below in the "Statistical section" [20].

MRD assessment by nested PCR

Molecular analysis was performed in a central highly experienced translational laboratory, according to a previously described nested-PCR approach [9,19,21]. Overall, 104 patients had adequate diagnostic material for molecular evaluation and a molecular marker was identified in 73 patients (65 had translocated BCL2 and 8 clonal IGH gene rearrangement as molecular marker). Among 73 patients with a molecular marker, 13 were not assessed for the following reasons: early toxic death, no CR, and inadequate diagnostic material for subsequent assessment. Thus, molecular response was investigated in 60 patients.

Long-term follow-up

The first outcome analysis was performed in 2008 [9]. Overall, 134 high-risk FL cases were analyzed. Only two patients (both CHOP-R arm) were censored as "lost to follow-up" at the moment of analysis, after a follow-up of 23 and 6 months, respectively. Recently, the long-term outcome of patients enrolled in this prospecti ve study has been updated. As of February 2017, updated data were obtained from 28 out of 29 participating centers regarding 119 (87.5%) out of 134 evaluable patients of the study protocol. Patients alive at the last follow-up have been followed for a minimum of 11 years and up to a maximum of 16 years. Overall, besides the two patients lost to follow-up at 6 and 23 months,

respectively, three more patients were lost to follow-up while in CR at 4 and 5 years from therapy; an additional 10 patients were lost to follow-up while in CR after a minimum of 8 years or more since therapy. All 15 patients lost to follow-up at the final update in February 2017 were censored as "lost to follow-up" at the time of their last contact.

The update was made by taking information on the following from 28 out of 29 participating centers regarding the clinical status of each patient entered in the prospective trial: status alive or dead or lost to follow-up, with the date of death or last follow-up alive; cause of death, i.e., lymphoma progression, secondary neoplasm, non-neoplastic late fatal complications, or other causes; occurrence of secondary hematopoietic or non-hematopoietic neoplasm; or disease status at last follow-up alive, i.e., continuous first, second or more CR

Study end-point and statistical analysis

The primary end-point was originally established as event-free survival (EFS), defined as the time from entry into the clinical trial and random assignment until progression/relapse/death from any cause, whichever occurred first, according to criteria published at the time of study launch [20]. A sample size of 246 patients (123 per arm) had been calculated to detect a 20% absolute increase (from 35%-55%) in 3-year EFS. A single interim analysis was planned, including the 120 patients who completed the treatment before March 24, 2005. R-HDS showed a significant EFS improvement (29% absolute increase, from 35%-64%), compared to CHOP-R ($p < 0.001$); this result led the steering committee to stop enrollment on May 30, 2005 [9].

Secondary end-points, again in the original protocol, were Overall Survival (OS), progression-free survival (PFS), and disease-free survival (DFS) [20]. The DFS curves for patients who achieved CR were calculated from CR date to relapse, death from lymphoma, or the last day of follow-up. Other secondary end-points were response rate, cumulative incidence of secondary myelodysplasia/acute myeloid leukemias (sMDS/AML) and solid tumors, rate of molecular remission (MR), and its impact on PFS. Alive patients were censored at the date of last contact (February 2, 2017), providing a median EFS and OS follow-up time of

13.01 years (range 0.5-16.6, interquartile range 11.8-14.7). All analyses were done on an intention-to-treat basis.

Survival curves were estimated by the Kaplan Meier method according to the revised response criteria published in 2007 and compared using the log-rank test [22-24]. EFS, OS, PFS, and DFS were analyzed by the Cox proportional hazards model, comparing the two treatment arms (R-CHOP vs. R-HDS) by the Wald test and calculating 95% confidence intervals [25]. The following covariates were tested as risk factors: age, sex, treatment arm, histologic grade, Ann Arbor stage, aaIPI score, FLIPI score (retrospectively assigned), "B" symptoms, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase, bulky disease (>5 cm diameter), spleen, bone marrow and extranodal involvement, MR rate, and achievement of CR/CR unconfirmed only for OS (this predictor was treated as a time-dependent covariate).

The cumulative incidences (CIs) of sMDS/AML and solid malignancies in the whole cohort and stratified by the treatment arm were estimated at 5, 10, and 13 years from diagnosis. The Gray test was used to compare the CI curves in the presence of a competing risk (defined as death from any cause except for sMDS/AML or solid tumors) [26].

Patient characteristics were estimated using the Mann Whitney test for continuous variables and the Fisher's exact test for categorical ones; all descriptive results for continuous variables are expressed as the medians (ranges).

All reported P values were two-sided, at the conventional 5% significance level. Data were analyzed as of January 2018 using R 3.4.3 [27].

CONSORT DIAGRAM, detailing the progress of 136 enrolled patients through the phases of the randomised trial