Lymphoma - Clinical 1

FRONTLINE TREATMENT WITH THE COMBINATION FLUDARABINE-LYMPHOMA - CLINICAL 1

A Ferrari, M Goldania, F Merli, V Callea, F Ilarucci, C Stelitano, M Russo, F Mazza, S Luminati, L Marcheselli, M Brugiatelli, D Luisi, F Rossi, B Olivero, G Lambertenghi Deliliers, M Federico, L Baldini

"UO Ematologia, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy; "UO Ematologia 1, Ospedale Maggiore Policlinico, Milan, Italy; "Servizio di Ematologia, Azienda Ospedaliera Bianchi-Melacrino-Morelli, Reggio Calabria, Italy; "Dipartimento di Ematologia ed Oncologia, Azienda Ospedaliera-Napoli, San Giovanni a Carbonara, Naples, Italy; "Dipartimento di Oncologia e Ematologia, Università degli Studi di Modena e Reggio Emilia, Modena, Italy; "Dipartimento di Oncologia e Ematologia, Università degli Studi di Pavia, Pavia, Italy; "Dipartimento di Oncologia e Ematologia, Università degli Studi di Torino and CPO Piemonte, Torino, Italy; "Pathology Unit, Spedali Civili Hospital, Brescia, Italy"

Background. Indolent non-follicular lymphomas (Nf0-NHL) include small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPC), marginal zone lymphoma (MZL). This heterogeneous group show different presenting features, behaviour pattern and treatment outcome. This subset of lymphomas has been relatively poorly investigated, and only retrospective studies or prospective trials involving limited series have so far been published. Aims. In 2002 the Gruppo Italiano Studio Linfomi (GISL) initiated LL02 prospective multicenter phase II trial, with the aim to evaluate the efficacy and safety of FC combination as front-line therapy of Nf0-NHL patients. Methods. Between July 2002 and September 2006, 63 adult patients affected by Nf0-NHL in active disease phase, were consecutively enrolled in 12 GISL hematological centres. After histologic revision, 61 patients could be enrolled in the study (36 males and 25 females, median age 64 yrs, range 40-75). The series included 22 cases of SLL, 11 LPC, 25 MZL, 3 CD5 negative NHL cases. Patients were treated with a dose of 25 mg/sqm Fludarabine plus 250 mg/sqm Cyclophosphamide administered intravenously daily for 3 days; each cycle was repeated every 28 days for 6 courses; an intermediate evaluation was performed after the third cycle. During the treatment patients received oral trimethoprim-sulphametoxazole and fluconazole prophylaxis. Results. Two patients were excluded because no further information after registration have been obtained. Six patients were withdrawn before the intermediate evaluation for early toxicity: 2 lethal infectious episodes (WHO grade 4), 3 haematological toxicities (WHO grade 3-4) and 1 renal toxicity (WHO grade 3). The remaining 53 patients were evaluable. At the median evaluation the ORR percentage was 83% with a 40.6% of complete remission (CR) and 64.4% of partial remission (PR). Among the 53 remaining patients, 43 completed the planned treatment of six cycles, 3 five cycles, 3 four cycles; 2 three cycles and 1 progressed after first cycle. At the final evaluation the ORR percentage was 83% with a 40.6% of CR (24 pts) and 42.3% of PR (35 pts); three patients were in progressive disease (5.1%) and one in stable disease (1.6%). On the basis of intention to treat analysis, after a follow-up of 60 months, the median overall survival (OS) was 64%, the progression free survival (PFS) was 54% and the failure free survival was 59%. The median remission duration was 26 months. After a median follow up of 36 months, mortality was 22% (17/61); among them, it was related to disease relapse/progression (35%), sepsis (29%), second tumor (18%), cerebrovascular event, respiratory insufficiency and other causes (6%). About the toxicity profile, the major toxicity was hematological with a 18% cases of WHO grade III or IV anemia, 54% neutropenia and 11% thrombocytopenia. The 10% of patients had an infectious episode of WHO grade III-IV. Conclusions. FC chemotherapy is a useful chance for advanced untreated non follicular low-grade NHL, with an optimal ORR, CR and PFS. OS is not significantly improved in comparison with Fludarabine alone or with standard therapy, even though the quality of responses was better. Infective (2 early deaths) and haematological (2 cases of WHO grade III-IV toxicity, causing the interruption of the planned treatment in a significant subset of patients, suggest an accurate selection and a careful monitoring during the therapy.

0270

EFFICACY AND SAFETY OF BORTEZOMIB AND RITUXIMAB ASSOCIATION IN RELAPSED/REFRACTORY INDOLENT NON-FOLLICULAR AND MANTLE CELL LYMPHOMA: FINAL RESULTS OF PHASE II STUDY BY INTERGRUPPO ITALIANO LINFOMI


‘On behalf of Intergruppo Italiano Linfomi (III), Torino, Italy; ‘Unit of Cancer Epidemiology, University of Torino and CPO Piemonte, Torino, Italy; ‘Pathology Unit, Spedali Civili Hospital, Brescia, Italy’

Background. Bortezomib alone or in combination with Rituximab has shown clinical benefit in treatment of Mantle Cell Lymphoma (MCL) and Marginal Zone Lymphoma (MZL). Aims. To evaluate safety and efficacy of Rituximab and Bortezomib combination in relapsed/refractory indolent non-follicular lymphoma and MCL, not eligible to high-dose chemotherapy. Patients and Methods. The study was a phase II multicenter trial according to Simon’s design. Inclusion criteria were: age 18-75 years, histological proven relapsed (> 1 year from the last therapy) or refractory (<1 year) indolent non-follicular (linfocytic lymphoma, LL, or MZL) and MCL after 1-4 lines of therapies. Treatment plan was: one course of four weekly intravenous bolus of 1.6 mg/sqm Bortezomib in combination with four infusion of 0.75 mg/sqm Rituximab followed by two courses of four weekly bolus of 1.6 mg/sqm Bortezomib. Patients with complete (CR), partial remission (PR) and stable disease at the intermediate evaluation were planned to be given three further courses with the same schedule. Results. From September 2006 to March 2008, 55 patients entered into the study. Histology revision was performed by three expert pathologists. Forty-nine patients fulfilled inclusion criteria and were evaluable. Clinical characteristics were: median age 65 (50-74) years; 16 LL, eight MZL, 25 MCL; 42 stage III/IV; 33 bone marrow involvement; 20 at intermediate-high/High IPI risk. Thirty-eight patients performed > two prior lines of chemotherapy; 34 were Rituximab-pretreated; 21 refractory and 28 relapsed disease. Overall Response Rate (ORR) was 53% (CR 26.5%, PR 26.5%); no response 48% and 4% off therapy for other causes. ORR by histology was: 37% in LL, 50% in MZL and 64% in MCL. ORR was not adversely affected by Rituximab pretreatment. Rituximab-pretreated 62% and Rituximab-naive 53%. ORR was higher in relapsed patients compared with refractory ones: 64% and 58% (p=0.06). With a median follow-up of one year, Overall Survival was 89% (95%CI 75-95) and 1-year Progression free survival (PFS) was 45% (95%CI 30-58) (Figure 1A). One-year PFS was 50% for MZL and 37% for LL (Figure 1B).
GRP78/Bip (glucose regulated protein 78/immunoglobulin heavy-chain binding protein) and OCT1/SLC22A1 (organic cation transporter 1/solute carrier family 22, member 1) are linked to drug resistance in solid tumors. There are no data about role of these proteins in AML. **Aims.** The main objective of this study was to compare the expression of GRP78 and OCT1 mRNA between non-MS AML patients and healthy individuals. **Methods.** Using quantitative reverse transcriptase PCR, the mRNA expression of two genes GRP78 and OCT1 was measured. Bone marrow samples of 83 AML patients (median age 49 years, range 19-84) taken at diagnosis, comprising all subtypes on the basis of FAB classification (without M3 subtype) were assessed. The control group consisted of 8 bone marrow aspirates from healthy individuals. The relative quantitation was indicated by cycle threshold (Ct) values. The Ct value of the target genes was normalized (ΔCt) to the Ct value of the ABL gene of the samples. **Results.** GRP78 and OCT1 mRNA were expressed in all samples. A statistically significant (P=0.00001) decrease in OCT1 mRNA expression was observed in AML patients compared with control group (ΔCt 7.382 SD 2.21 vs. ΔCt 3.06 SD 1.269 respectively). GRP78 mRNA expression was higher in AML samples than in healthy individuals (ΔCt -4.791 SD 0.75 vs. ΔCt -5.097 SD 0.453 respectively), although there was no statistically significant difference (P=0.212). There was also no statistical correlation between the expression levels of GRP78 and OCT1 in AML patients and complete remission status. **Conclusion.** Our preliminary data indicate differences in expression of GRP78 and OCT1 mRNA in AML patients compared to healthy individuals. Further studies should be undertaken to demonstrate their clinical impact in acute myeloid leukemia.

### 1251

**MYELOID SARCOMA: CLINICAL CHARACTERISTICS AND PROGNOSIS**

O Baranova, N Falaleeva, S Lunina, A Shirin, A K vaginal, M Volkova N.N. Blokhin Cancer Research Center RAMS, Moscow, Russian Federation

**Introduction.** Myeloid sarcoma (MS) is a rare hematologic neoplasm which was defined by WHO classification as a separate myeloid tumor. Any site of the body other than the bone marrow (BM) can be affected by this tumor. MS may occur de novo and as the manifestation of relapse in patients (pts) with previously diagnosed acute myeloid leukemia (AML). The aim of the study was to investigate clinical characteristic and prognosis in pts with de novo MS. **Methods.** We observed 121 pts with AML treated at N.N. Blokhin Cancer Research Center RAMS from 2000 to 2010. In this study we included pts with de novo MS with extramedullary lesions without BM involvement (according to BM smears and BM biopsies examinations). MS diagnosis was based on histological and immunohistochemical tumor mass studies. Immunohistochemical study was performed with monoclonal antibodies for MPO, lysozyme, CD33, CD13, CD117, CD15, CD68, CD34, TdT, PGM-1.

**Results.** MSs de novo were revealed in 8 pts (6.6%) and as relapse of AML in 2 pts (1.7%). Median age of pts with MSs de novo was 39 years (range 17-61). Male: female ratio - 5.5. MSs localizations: 3 cases of genital system lesions (2 - vagina and regional lymph nodes, 1 - uterus, ovary and regional lymph nodes); 1 case - bulky tumor mass in soft tissues of supraclavicular, subclavian, axillary, scapular areas and region- nal lymph nodes; 1 case - shin bone and soft tissues of this area; 1 case - neck and supraclavicular lymph nodes; 1 case - bulky tumor mass in mediastinum, lesions of pericardium, pleura, lung, mediastinal lymph nodes; 1 case - small bowel (with features of its acute obstruction).

**Treatment.** MS consisted of the regimen for AML: induction therapy "3+7+7" (idarubicin 12 mg/m2 d 1-3, Ara-C 200 mg/m2 d 1-7, Etoposide 75 mg/m2 d 1-7), 3 cycles of consolidation therapy "HAI" (idarubicin 12 mg/m2 d 4, plus Ara-C 8 g/m2 every 12 hours d 1, 3, 5), 4 cycles of post-consolidation therapy "1+5+5" (idarubicin 12 mg/m2 d 1, Ara-C 200 mg/m2 d 1-5, Etoposide 75 mg/m2 d 1-5). All pts received intrathecal Mtx + Ara-C + Dexa. In 1 case of small bowel acute obstruction the first step of treatment was surgical. 2 pts received radiotherapy on tumor lesions areas. 1 patient received high-intensity chemotherapy and autologous stem cell transplantation after 2 cycles of consolidation therapy "HAI". Follow-up period was 16 months. Median OS and median RFS were not reached. 1 case of relapse was registered. RFS was 67% at 3 years follow-up period. Remission duration ranged from 1+ to 59+ months, life expectancy ranged from 16 to 61+ months, all pts are alive at the time of analysis. **Conclusion.** MSs are characterized by various clinical features. Intensive chemotherapy for AML makes it possible to obtain encouraging results in treatment of MSs.

### 1252

**CORRELATING OUTCOMES AND LONG-TERM SURVIVAL FOLLOWING CHEMOTHERAPY IN NORMAL KARYOTYPE AML WITH MOLECULAR RISK - SINGLE CENTRE EXPERIENCE**

LC Lim, GF How, Y Loh, GC Wong Singapore General Hospital, Singapore, Singapore

**Background.** Patients with normal karyotype AML (N K AML) are a heterogeneous group and assessment for molecular genetic aberrations are important for prognostic differentiation. Presence of mutation involving internal tandem duplication of FLT3 gene (FLT3-ITDmut) is reported in 20-30% NK AML and is associated with poor outcome. In contrast, prognosis is considered good for patients who are FLT3-ITDmut negative but have mutations of NPM1 (NPMmut) or CEBPA (CEBPAmut) genes. **Aims.** We analyse the molecular profile in relation to therapeutic outcomes following chemotherapy in 35Patients with NK AML treated between 2003-2007. **Methods.** Only patients less than 65 years old who received induction chemotherapy were included in study. Molecular analyses for mutations of FLT3-ITD, NPM1 and CEBPA were performed on bone marrow samples obtained at diagnosis. Standard induction therapy was idarubicin and cytarabine (IA3+7). Bone marrow assessments were performed on day 14 of induction and also upon recovery of neutrophil and platelet counts. Patients who failed to go into complete remission (CR) with 1 course of induction undergo a second cycle of IA3+7. Subsequent to achieving CR, further chemotherapy was administered with: 1 cycle of IA2+7 and 1 cycle of high dose cytarabine (HDAC). Following this, patients with persistent leukemia or who failed to go into CR after 1 cycle of induction chemotherapy or are FLT3-ITDmut positive undergo allogeneic stem cell transplant (alloSCT) if they have available sibling or match unrelated donors. All others undergo either autologous stem cell transplant (autoSCT), or 2 more cycles of HDAC. **Results.** The median age was 40 years (15-68 years) and median follow up 30 months (4 to 79 months). Of 35 patients, overall rate of CR after 1 cycle of induction chemotherapy (CR1) was 26/35 (74%). Nine patients (26%) required 2 cycles of induction chemotherapy following which 8 achieved remission but 1 remained refractory and died of sepsis. Responses to chemotherapy and outcomes were correlated with presence or absence of the 3 molecular genetic aberrations as indicated in Table 1. Conclusion. In absence of FLT3-ITDmut, NPMmut or CEBPAmut positivity predicts for good responses to induction chemotherapy. Long-term outcomes are excellent following consolidation chemotherapy in this group as 80% remain disease free at 5 years compared with 5-year DFS of 14% for FLT3-ITDmut positive or triple negative patients (P=0.02). AutoSCT for consolidation is a reasonable approach for FLT3-ITDmut negative but NPM1mut or CEBPA mut positive patients.

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**ACUTE MYELOID LEUKEMIA IN PATIENTS AGED 70 OR OLDER. EXPERIENCE AT A SINGLE CENTRE**

JN Rodríguez, E Martin, MV Moreno, A Palma, JA Quesada, A Chacón, MJ Romero, K Gómez, A García-Sola, JC Diéguez, A Amian, A Fernández-Jurado Hospital Juan Ramón Jiménez, Huelva, Spain

**Background.** The management of old patients with acute myeloid leukemia remains controversial, specially in those cases affecting very old patients (aged ≥70) in which the dilemma therapeutic abstention vs. treatment (with low or high intensity ones) is a major subject. **Aims.** We present the experience in our centre with this group of patients in the period 1990-2009. **Methods.** During the period of study 85 cases were