Hodgkin lymphoma

494 INFLAMMATORY MARKERS ASSESSMENT AT DIAGNOSIS CAN IMPROVE THE RISK ASSESSMENT OF HODGKIN LYMPHOMA PATIENTS

C. Vetro[1], A. Romano[1], P. Fiumara[1], D. Donnarumma[1], A. Chiarenza[1], A. Figuera[1], A. La Fauci[1], V. Innao[1], G. Uccello[1], G. A. Palumbo[1]
[1]*Divisione di Ematologia, Ospedale Ferrarotto, Catania, Italy*

Background: Inflammation dominates both the clinical pictures of Hodgkin Lymphoma (HL). The interim-PET findings seem to reflect the chemo-sensitivity more than the real tumor eradication, related to the ability of chemotherapy to reduce the inflammatory microenvironment. In the present study, we evaluated the role of inflammation markers such as ESR and Ferritin in predicting the interim-PET results and the outcome.

Patients and Methods: Sixty-seven patients with HL were treated with ABVD as first line and PET was performed at diagnosis, after two cycles (interim-PET), and at the end of treatment. PET images were interpreted visually according to Dann et al., 2010. 43/67 (64%) patients were at stage I-II, 5 of them (11.6%) had a positive interim-PET and 2 relapsed although their early shift to BEACOPP regimen. Three more patients have relapsed although their interim-PET was negative. 24/67 (36%) patients were at stage III-IV. Two of them had a positive interim-PET and they relapsed notwithstanding early BEACOPP switch. Three more patients have relapsed although their interim-PET was negative.

Results: ESR levels were generally upper than normal values, with a median of 47 mm/hr and a range between 4 and 122 mm/hr. ESR was correlated with the interim-PET positivity after 2 cycles of ABVD in early-staged (I-II) males with unfavorable features (median=46 mm/hr; range= 26-99 mm/hr; p=0.002). Ferritin levels showed a wide variation with a median of 188.5ng/mL and a range between 11.3 and 4,982 ng/mL. Independently from the stage, we found a negative correlation between ferritin and absolute count of circulating lymphocytes (r=-0.2, p=.02), and a positive correlation with markers of systemic inflammation (ESR, CRP, albumin, r=0.5, p=0.03). Eighteen patients in advanced-stage had very-high levels of ferritin (>500 ng/mL) at diagnosis. Although we did not find any correlation between ferritin levels and interim-PET positivity, patients with high ferritin levels had a reduced PFS compared to subjects with normal or moderately increased ferritin, independently from IPS score (respectively, 20.13 months vs not achieved median) (log rank test; p=0.026).

Conclusion: Taken together, our observations suggest how the evaluation of ESR and ferritin at diagnosis can add prognostic information. In particular, ESR may be useful in predicting interim-PET positivity in early stage, while ferritin evaluation might help in assessing the prognosis of advanced stage HL patients independently from the interim-PET assessment.

495 POLYMORPHISM OF GSTP1 GENE AND PROGNOSIS OF HODGKIN'S LYMPHOMA IN UKRAINIAN INDIVIDUALS

N. M. Svergun[1], I. A. Kryachok[2], N. M. Khranovska[1], O. I. Novosad[2], I. B. Titorenko[2], V. K. Pozur[3], T. V. Kadnikova [2], O. V. Aleksik [2], K. S. Filonenko [2], A. V. Martynchik[2], H. O. Gubareva [2], Y. V. Kushchevyy[2], Y. V. Pastushenko[2]
[1]*Laboratory of Experimental Oncology, National Cancer Institute, Kyiv, Ukraine,* [2]*Oncohematological Department, National Cancer Institute, Kyiv, Ukraine,* [3]*Educational and Scientific Centre «Institute of Biology», National Taras Sevchenko University of Kyiv, Kyiv, Ukraine*

Modern risk-adapted treatment regimens for Hodgkin's lymphoma (HL) include nitrogen mustards, anthracyclines, vinca alkaloids and epipodophylotoxins, which are metabolized by enzymes of the glutathione S-transferase (GST) system. GSTP1 is a member of the GST enzyme superfamily. The polymorphism of the GSTP1 gene causes the substitution of isoleucine to valine at amino acid codon 105 (Ile105Val). In this report we present the results of the study of the prognostic impact of genetic polymorphism of the GSTP1 gene in patients with HL.

The case group was comprised of 87 patients with HL (stages IA-IIA:33, stages IIB+III-IV:54) and 158 blood donors. Genomic DNA from peripheral blood was analyzed for GSTP1 genotype identification using TaqMan PCR allelic discrimination assays.

The distribution of the GSTP1 gene genotypes in both control and patient groups did not differ significantly from those predicted by the Hardy — Weinberg distribution. Observed Val allele frequency was 0.32, similar to previous reports on allele frequencies for healthy Caucasians. The frequency of the homozygous wild genotype of the GSTP1 was higher in patients with stages IIB+III-IV than in patients with stages IA-IIA (47, 2 % versus 35 %, P = 0.02). Complete response (CR) was achieved after first-line treatment in 65 patients. Among the patients who achieved CR, 13 relapsed during the period of observation: disease-free period 3- 6 months (8 patients) and 12-16 months (5 patients). We noticed that 69 % of patients with relapse (9 patients) were homozygous for wild genotype of GSTP1 gene. For patients with increasing number of Val alleles there was a trend for a better remission rate to first-line therapy (P = 0.12) and a lower risk for relapse (P = 0.09) in our cases, but it should be confirmed by further studies with larger cohorts of patients.

The obtained results suggest that the Ile105Val polymorphism of the GSTP1 gene is not directly involved in the development of HL, but homozygous wild genotype of this gene may be associated with the risk of relapse of HL in Ukrainian individuals. Hence the investigation of GSTP1 polymorphism is very promising, since it might provide a possible application of this genetic marker as an independent prognostic factor of HL.

496 HODGKIN' S LYMPHOMA; AN OUTCOME STUDY BASED ON SINGLE CENTER EXPERIENCE

C. Schiavotto[1], R. Cavazzina[1], M. Ruggeri[1], F. Rodeghiero[1]
[1]*Hematology Department, San Bortolo Hospital, Vicenza, Italy*

Introduction: The treatment of Hodgkin' s Lymphoma (HL) is considered one among the greatest success of cancer therapy with a cure rate of about 80 %. Thus sparing toxicity and quality of life became the main goals; long-term side effects may cause a mortality rate exceeding that from HL after 15 y of follow-up. However, while a large number of clinical trials based on very selected patients population are available, there are few data about the long-term outcome in unselected population. We reported here a single center experience collected in the last sixteen years.

Patients and Methods: Since April 1994 until December 2004, a total of 223 consecutive adult HL pts, M/F 114/109, median age 33 y (13-88) has been recorded. Stage I-II 161, III-IV 60, undetermined 2; B symptoms were present in 76, not reported in 2. Chemotherapy plus Radiotherapy (CT) were performed in 174, Cht in 35, RT in 9, no therapy in 5. 192 pts were treated with full-dose curative intent ABVD, MOPP/ABV, Stanford V, while 31 were approached with less intensive therapy/palliation based on CHLVPP, VBM or steroid. Young relapsing/refractory pts were trasplanted with autologous stem cell.

Results: After a median follow-up of 6 y (7d-16y), 191/223 (85%) obtained CR, 16 (8%) relapsed, 11 were refractory, 7 obtained PR; 14 (6%) died during induction or in palliation. 34/223 (15%) needed a second-line therapy; of them 12 (35%) obtained CR, 20 died for disease progression/toxicity, 1 was alive at the last follow-up with active disease, 1 refractory was lost at the last follow-up. We recorded a total of 44 deaths, 11 in CR, 33 for disease progression/toxicity. 28/223 were 65 y or older (13%); 4/28 were treated with palliation only for comorbidity and died after a median follow-up of 2 months, 24/28 were treated, 10 with full-dose ABVD, 14 with less intensive therapy. 18/24 obtained CR (75%), 3 relapsed, 4 died while on therapy, 1 was refractory, 1 obtained PR. At the last follow-up, 8/28 (28%) are alive in CR, 1 alive with active disease, 19 died.

Conclusions: Our results confirm brilliant worldwide reported data; OS of the whole population was 75% after 6 y of follow-up. 14 % of the whole population was treated with less-intensive therapy for comorbidity or pure palliation,. Induction death rate is higher than previously reported in clinical trial. Pts >= 65 y account for 43 % of the mortality rate; among them, only a minority (38%) were treated with full-dose ABVD, however a large quote obtained at least a transitory CR. Outcome of older pts seems to induce a limited influence on the HL whole population 's one

497 THE NEW CHEMOTHERAPY REGIMEN FOR HODGKIN LYMPHOMA

P. Dacenko[1], G. Panshin[1], V. Sotnikov[1], I. Albitski[1]
[1]*Radiation Therapy, Russian Scientific Center of Roentgenoradiology, Moscow, Russian Federation*

Background: The aim of this study was to improve the effectiveness of standard ABVD regimen for Hodgkin lymphoma (HL) by addition of etoposide and lomustine.

Materials and Methods: The CEA/ABVD chemotherapy regimen (baseline) was introduced in 2000. Chemotherapy was given weekly for 13 weeks as follows: doxorubicin 25 mg/m^2 on weeks 1, 2, 4, 5, 8, 9, 12, and 13; bleomycin 10mg/m^2 (maximum dose 15mg) vinblastine 6mg/m^2 (maximum dose 10mg) and dacarbazine 375mg/m^2 on weeks 1, 2, 5, 8, 9, and 13; lomustine 80 mg/m^2 and etoposide 100 mg/m^2 for three days on weeks 4, and 12. Bloc-chemotherapy CEA/ABVD regimen was introduced in 2007. Chemotherapy was given weekly for 17 weeks as follows: doxorubicin 25 mg/m^2 on weeks 1, 3, 5, 7, 9, 11, 13, 15, and 17; bleomycin 10mg/m^2, vinblastine 6mg/m^2 and dacarbazine 375mg/m^2 on weeks 1, 5, 7, 11, 13, and 17; lomustine 80mg/m^2 and etoposide 100mg/m^2 for three days on weeks 3, 9, and 15. One hundred seven patients with HL stage II - IV were treated: 12 patients with favorable, 39 patients with intermediate and 56 patients with unfavorable prognosis (GHSG). Sixty patients were treated with baseline CEA/ABVD, 47 - with bloc CEA/ABVD. Radiation

therapy (RT) was given after chemotherapy in all patients: involved field or involved node RT - 8 patients, extended field RT – 45, subtotal nodal RT – 54 patients.

Results: After a median follow-up of 4.1 years, the rates for 5-years freedom from treatment failure (FFTF) are 95.5%, and for 5-years overall survival (OS) - 93.7%. Four relapses and 5 deaths have occurred (2 – HL, 1 – hematologic toxicity, 1 – cardiovascular disease, 1- fatal pneumonitis). In CEA/ABVD baseline group (60 patients) with median follow-up of 6.6 years there were 3 relapses, 5-years FFTF - 94.7%, 5-years OS – 91.1%. In CEA/ABVD bloc group (47 patients) with median follow-up of 1.9 years, there was 1 relapse, 3-years FFTF - 96.4%, 3-years OS – 100%. Acute toxicity: myelosuppression constituted the major acute toxicity (107 patients), one death has occurred due to hematologic toxicity (1.7%). In the groups with CEA/ABVD baseline or bloc toxicity was tolerable with WHO grade 4 leucopenia in 25% and 44,7% of chemotherapy cycles, grade 3-4 anemias - in 13.3% and 25.5%, grade 3-4 thrombocytopenia - 20% and 19.1%. A total of 58 patients (54%) received G-CSF. Febrile neutropenia rate was 22%, infection rate - 11.5%, gastrointestinal toxicity - 5%. With a median follow-up of 4.1 years, there are no cases of second solid malignancy, leukemia or myelodysplasia.

Conclusion: CEA/ABVD chemotherapy with RT is highly effective in locally extensive and advanced Hodgkin's disease. It is important to compare this regimen with standard ABVD and BEACOPP chemotherapy.

498 AUTOLOGOUS STEM CELL TRANSPLANTATION IN RELAPSED NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA PATIENTS

H. Mocikova[1], J. Michalka[2], P. Stepankova[3], L. Raida[4], A. Wild[5], V. Vozobulova[6], Z. Kral[2], D. Belada[3], J. Markova[1], J. Mayer[2], K. Indrak[4], V. Koza[6], T. Kozak[1]
[1]Department of Clinical Hematology, Charles University Hospital Kralovske Vinohrady, Prague, Czech Republic, [2]Clinic of Internal Medicine – Hematology and Oncology, Masaryk University Hospital, Brno, Czech Republic, [3]Department of Hematooncology, University Hospital and Medical School, Hradec Kralove, Czech Republic, [4]Clinic of Hematooncology, Palacky University Hospital, Olomouc, Czech Republic, [5]Department of Hematology, F D Roosevevelt Hospital, Banska Bystrica, Slovakia, [6]Department of Hematooncology, Charles University Hospital, Pilsen, Czech Republic

Background: The role of autologous stem cell transplantation (ASCT) in relapsed nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is not well established.

The aim was to compare overall survival (OS) after therapy with or without ASCT in relapsed NLPHL patients (pts).

Patients and Methods: Overall 17 pts (12 relapsed NLPHL and 5 NLPHL transformed to diffuse large B cell lymphoma [DLBCL]) were treated with conventional chemo-radiotherapy and/or rituximab and 7 of them underwent chemotherapy BEAM (carmustine, etoposide, cytarabine, melphalan) and ASCT. Groups with or without ASCT were comparable in clinical characteristics (gender, age, clinical stage, number of NLPHL transformed to DLBCL, number of relapses and treatment lines). More cycles of rituximab were used in the group without ASCT (p=0.035).

Results: Median follow-up of 17 pts from diagnosis was 8 years. Out of 17 pts 15 are alive in complete remission and 2 transplanted pts with NLPHL transformed to DLBCL died: 1 after abdomen injury and 1 due to transplant-related complications. The 5-year progression-free survival after ASCT was 60 %. The 10-year OS of the whole group from diagnosis was 85.7 % and difference between the 10-year OS from diagnosis in the group with and without ASCT was not significant (p=0.302). Difference between the 5-year OS from the last conventional therapy compared to ASCT was not significant (p=0.527).

Conclusions: There was no difference in OS when compared ASCT and conventional therapy approaches including rituximab in multiple relapses of NLPHL. ASCT can be safely used in these pts although relapses are seen even after ASCT.

499 INTENSIFIED CHEMOTHERAPY BEACOPP ESCALATED FOLLOWED BY ABVD AND INVOLVED FIELD RADIOTHERAPY IN PATIENTS WITH EARLY UNFAVORABLE HODGKIN'S LYMPHOMA: SINGLE CENTER EXPERIENCE

A. Sykorova[1], P. Stepankova[1], D. Belada[1], D. Klimes[2], L. Smolej[1], J. Maly[1]
[1]2nd Department of Internal Medicine - Department of Haematology, Charles University, Faculty of Medicine and University Hospital, Czech, Hradec Kralove, Czech Republic, [2]Institute of Biostatistics and Analyses, Faculty of Medicine and Faculty of Science of the Masaryk University, Brno, Czech Republic

Background: Intensified therapy 2 cycles of BEACOPP escalated followed by 2 cycles of ABVD and 20 Gray (Gy) of involved field radiotherapy (IFRT) is the new standard therapy for patients (pts) with early unfavorable Hodgkin's lymphoma (HL) according to the results of HD 14 study by German Hodgkin Study Group (GHSG). Aims of the study: Evaluate efficacy of the therapy with regard to dose intensity of chemotherapeutic regimens.

Patients and Methods: Between January 2004 and November 2010 we treated 21 younger pts (< 60 years) with newly diagnosed early unfavorable HL with intensified therapy. Pts received 2 cycles of BEACOPP escalated followed by 2 cycles of ABVD and IFRT 20 or 30 Gy. Therapeutic response was evaluated using revised response criteria by Cheson (2007). Intensity of chemotherapy was assessed by the calculating the average relative dose-intensity (ARDI) and total relative dose-intensity (ATRDI) for each constituent (without vincristine in BEACOPP escalated) and for each regimen. Secondary endpoints included toxicity of therapy, dose delays and use of granulocyte-colony stimulating factor (G-CSF).

Results: The median age of the pts was 30 years (range, 20-50), Ann Arbor stage II/IIE/IIS was present in 17/2/2 pts. Nodular sclerosis was the predominant histological subtype (18 pts, 86%). Large mediastinal mass/extranodal involvement were present in 4/2 pts. The dose of RT was 20 Gy (8 pts, 38%) or 30 Gy (11 pts, 52%). Eighteen pts (85%) achieved complete remission, 3 pts will undergo final restaging. Median follow up was 20 months (range, 2-70). Myelotoxicity was the most common adverse event with grade 3 and 4 thrombocytopenia in 6 pts (28%). Grade 3 infections according to Common Toxicity Criteria v. 3.0 were documented in 3 pts (14%). Use of G-CSF support was obligatory in BEACOPP escalated and optional during ABVD regimen. Eighteen pts (85%) needed G – CSF support during ABVD. Median of G – CSF use (1 dose of 48 MIU) was 10,5 doses (range, 6-15) for 2 cycles escalated BEACOPP, 6 doses (range, 1-18) for2 cycles ABVD. Scheduled duration of sequential chemotherapy was 14 weeks. Median duration of treatment administration was 14 weeks (range, 14-17). The treatment prolongation ≥ 7 days occurred in 8 pts (38%). ARDI was 99.4% (range, 94.7 - 104.3) for BEACOPP, 99.8% (range, 94-120.3) for ABVD, respectively. ATRDI was 97.3% (range, 88-104.3) for 2 cycles of BEACOPP escalated and 93.6% (range, 78.2-103) for 2 cycles of ABVD, respectively. Lower dose intensity of chemotherapy was caused by delayed timing of chemotherapy (leucopenia, infections).

Conclusion: Our data confirm that combination of BEACOPP escalated and ABVD followed by IFRT is a highly effective therapy for pts with unfavorable HL. This approach is aggressive and associated with high risk of hematological toxicity and risk of reduction of TRDI. Early identification of pts at high risk of delay might be an important and rational way to use recombinant G–CSF support to ensure timely delivery of planned chemotherapy.

500 FERTILITY IN YOUNG FEMALE HODGKIN DISEASE PATIENTS AFTER ESCALATED BEACOPP REGIMEN

W. Jurczak[1], K. Mosurska[1], W. Pabian[1], A. Giza[1], M. Sobociński[1], T. Ogórka[1], A. B. Skotnicki[1]
[1]Dpt of Haematology, UJ CM, Kraków, Poland

Introduction: Escalated BEACOPP regimen is an established standard in high risk Hodgkin Disease (HD) patients. In order to reduce its long lasting side effects, over 70% of patients (good responders in early PET scans performed after 2-nd cycle) were de-escalated to ABVD. In the whole cohort, OS and EFS at 5 years (96 and 90% respectively) were comparable to original GHSG results, with relatively low incidence of MDS (1/119 cases). In this abstract female infertility was retrospectively assessed.

Material and Methods: 62 young females (average age: 27, 17-44) completed 2-8 series (average 3.8) of escalated BEACOPP regimen by 2009. Hormonal function of gonads was indirectly assessed by FSH levels in 55 patients. Cases with FSH > 15mIU/ml were regarded unfertile. We were able to contact 46 patients to question them retrospectively about premature menopause symptoms and address the fertility issues.

Results: During chemotherapy 59 (95.2%) of our patients experienced transient menstrual cycle irregularities/ amenorrhea. All cases with FSH > 15mIU/ml (N= 21, 33.87%) manifested symptoms of premature menopause. We confirmed 9 pregnancies in 34 patients who declared an attempt to conceive a child after the chemotherapy. Medium period of time from chemotherapy to conception was 26.6 months (2-63). They received 3.88 (2-8) cycles of escalated BEACOPP and - in 3 cases with refractory/relapsing disease - ESHAP followed by ASCT. In 3 cases, FSH values indicated premature menopause (medium FSH=62 mIU/ml, 34.1 – 107 mIU/ml) and were treated over 12 months with hormonal replacement therapy.

Conclusions:

1. PET guided therapy allowing for dose de-escalation decreased the risk of infertility in HD patients treated by escalated BEACOPP regimen from 95% (in original GHSG studies) to at most 76%.

2. Premature menopause after chemotherapy was inadequately diagnosed (based on FSH levels and clinical symptoms) in at least 3 cases (14% of our patients).Table 1

Pregnant patients after escalated BEACOPP chemotherapy - summary of clinical symptoms and hormonal assessment.Menstrual status&Premature menopause&FSH [mIU/ml] \cr no abnormalities (n = 1)disorders lasting < 6 months (n = 4)disorders lasting > 6 months (n = 4)&Absent (n=1)Present (n= 8)&Normal 4.05 (2.1-15.3) (n = 6)>15 (34, 45, 107) (n = 3)