ORAL CHEMOTHERAPY: AN INNOVATIVE CHOICE

L. Bergui,[1] M. Scaldaferri,[4] E. Sciorsci,[4] G. Valinotti,[4] A. Ghiggia,[2] F. Cavallo,[1] S. Ferrero,[1] P. Ghione,[1] L. Castelli,[2] R. Torta,[3]

[1]*Division of Hematology, University of Torino, AOU Città della Salute e della Scienza di Torino, Torino;* [2]*Dipartimento di Psicologia, Università di Torino, Torino;* [3]*Dipartimento di Neuroscienze, Psicologia Clinica e Psico-Oncologia Università di Torino, Torino;* [4]*SC Farmacia Azienda Ospedaliera Città della Salute e della Scienza di Torino, Torino, Italy*

Despite improvement of lymphoma treatments, many patients still relapse, the majority of whom being elderly and reluctant or unable to receive iv chemotherapy. It is known that treatment with all-oral protocols lowered management costs, without impairing efficacy. In our study, outpatient oral chemotherapy schemes were specifically designed to offer a well tolerated and easy to administer therapeutic option. This program was planned by clinicians, psycho-oncologists and hospital pharmacists, the latter providing detailed information on drugs management. Molecules of widespread use and moderate cost were employed: NIET (Idarubucin30mg/sqm d1, Procarbazine 100mg/sqm d1-4, Etoposide100mg/sqm d1-4, Dex 20 mg d1-4), FC (Fludarabine 25 mg/sqm, Cyclophosphamide 150 mg/sqm d1-4), CD (Cyclophosphamide 100 mg/sqmx2d1-5 Dex 20 mg d1) and Chlorambucil 10mg d1-10. A total of 100 patients were evaluated: median age at treatment start was 77 y (33 – 95), the majority of patients were unfit (37) or frail (46) according to multiparametric geriatric evaluation. Fifty-five patients had indolent lymphoma (Chronic Lymphocytic Leukemia, CLL 29; Small Lymphocytic Lymphoma, SLL 12; others 14), 45 had aggressive lymphoma (Diffuse Large B cell Lymphoma, DBLCL 28, Mantle Cell Lymphoma,MCL 6 and T-cell lymphoma 6, others 5). Twenty-nine patients had no prior treatment, 49 underwent 1-4 previous lines of therapy, 11 patients 5-6 lines and 11 patients more than 6 lines. Efficacy and toxicity were evaluated on 62 patients receiving at least 3 cycles of therapy: 74% had an objective benefit, 14% had stable disease, 12% had a progressive disease. G3-4 haematological toxicity was detected in 12 cases and non-haematological G3-4 toxicity in 2. Psycho-oncological tests revealed that 72% of the patients had a HADS (Hospital Anxiety and Depression Scale) score below the cutoff, both at T0 and at T1, suggesting low psychological distress. What is more, 88% of the patients judged positively the information about the treatment and the presence of the pharmacist. These data showed that chemotherapy does not negatively impact the psychological status. Our all-oral approach is an efficient alternative to traditional iv chemotherapy for elderly and frail patients with no cure expectation. The therapy shows some efficacy, improves the comfort from symptoms, is well tolerated and has restrained costs.

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VITAMIN D DEFICIENCY AND SUPPLEMENTATION IN ITALIAN PATIENTS WITH B CELL LYMPHOMAS TREATED WITH RITUXIMAB-CONTAINING CHEMOTHERAPY

M.C. Tisi, S. Bellesi, E. Maiolo, F. Corrente, E. Alma, F. D'Alò, S. Hohaus

Istituto di Ematologia, Università Cattolica del Sacro Cuore, Roma, Italy

Data from the German RICOVER-60 study indicate that Vitamin D deficiency is a risk factor in elderly patients with diffuse large B-cell lymphomas (DLBCL) treated with Rituximab-containing chemotherapy (R-CHOP) (Bittenbring *et al.*, J Clin Oncol 2014). A retrospective analysis of cohorts of follicular lymphoma (FL) patients showed an inferior survival also for FL patients (Kelly *et al.*, J Clin Oncol 2015). *In vitro* data suggest that Vitamin D supplementation could enhance rituximab-mediated cytotoxicity. We measured prospectively Vitamin D levels in an Italian cohort of 87 newly diagnosed patients with B cell lymphomas (62 patients with DLBCL, 25 patients with FL) who were candidates for Rituximab-containing chemotherapy. Vitamin D levels were considered deficient (<10 ng/ml) in 37 patients (43%), insufficient (10 to 30 ng/ml) in 44 patients (51%), and normal (>30 to 100 ng/ml) in 6 patients (7%). There was no difference between FL and DLBCL patients. Looking at patient characteristics we found a trend for lower Vitamin D levels with older age (p=0.06). In addition, there was a significant seasonal variation of Vitamin D levels with lower levels in the winter months. Considering the possible influence of Vitamin D levels on *in vitro* rituximab-mediated cellular cytoxicity by NK cells, we implemented a substitution regimen to achieve Vitamin D levels early during treatment. We supplemented Vitamin D (cholecalciferole) in a daily dose of 25000 U for a period that varied according to the initial Vitamin D levels and subsequently continued maintenance with cholecalciferole 25000 U once a week. A second determination of Vitamin D levels after a median of 1.1 month in 24 patients showed a significant increase of Vitamin D levels from 14+1.4 ng/ml to 27+1.9 (mean+SEM, p=0.001). Supplementation resulted in rapid normalization of Vitamin D levels in 10/24 patients (42%) No episodes of hypervitaminosis or hypercalcemia were observed. In 13 patients without supplementation, Vitamin D levels showed no significant variation (15+3 ng/ml at diagnosis *vs* 12+1.6 ng/ml during therapy). Studies of Vitamin D levels on NK cell population are ongoing. We conclude that Vitamin D deficiency is frequent in patients with aggressive and indolent B cell lymphomas also in Central Italy. Vitamin D levels can be rapidly normalized using a daily substitution regimen. This may help to improve efficiency of rituximab-containing treatment regimens.

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NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMAS TREATED WITH RITUXIMAB - CHOP: DEFINITION AND VALIDATION OF A PROGNOSTIC SCORE MODEL BASED ON MYC, BCL2 AND BCL6 EXPRESSION IN IMMUNOHISTOCHEMISTRY

A. Castellino,[1] B. Botto,[1] P. Riccomagno,[1] A. Chiappella,[1] M. Novo,[1] L. Zattera,[1] F. Cavallo,[2] P. Ghione,[2] A. Evangelista,[3] C. Ciochetto,[1] G. Ciccone,[3] M.S. Scalzo,[4] R. Chiarle,[5] D. Novero,[4] U. Vitolo[1]

[1]*SC Ematologia;* [2]*SC Ematologia, U;* [3]*Servizio di Epidemiologia dei Tumori, CPO Piemonte;* [4]*Servizio di Anatomia Patologica, AOU Città della Salute e della Scienza, Torino, Italy;* [5]*Department of Pathology Children's Hospital, Boston, USA*

Overexpression of MYC and BCL2 and low expression of BCL6 assessed by HIC have been reported as negative prognostic factors in DLBCL. We recently presented (Botto B, ASH 2014) a pilot study, that suggested a prognostic score based on overexpression of MYC, BCL2 and low expression of BLC6, assessed by HIC, in a retrospective cohort of 69 *de novo* DLBCL, with an high proliferation index (MIB1 >70%), treated with R-CHOP between 2010 and 2013. The aim of the present study was to expand the analysis and validate this prognostic score in a larger retrospective cohort of DLBCL, without restrictions of MIB1. *de novo* DLBCL patients, treated with R-CHOP between 2003 and 2013 were included. Cases enrolled in the previous pilot study were considered as control group. Samples were investigated using TMA sections for MYC, while BCL2 and BCL6 staining had been evaluated at diagnosis. Positivity was defined for MYC and BCL2/BCL6 expression by immunostain if >40%, >40% and 25% of cells showed positive expression, respectively. FISH is ongoing. Among 119 patients eligible, 99 were evaluable, 20 were not due to missing clinical data. Clinical characteristics were: median age 63.5 years (IQR 52;73), 66 (68%) stage III-IV, 27 (28%) with LDH upper normal and 30 (30%) with IPI >2. These characteristics are superimposable to those of the pilot study, a part for a lower rate of IPI>2 (30% *vs* 67%). Median MIB1 at diagnosis was 70% (IQR 60-85). At the moment of the present analysis, MYC was investigated in 45/99 cases and an overespression was detected in 10 (22%). BCL2 and BCL6 were analyzed in 77 and 74 cases, with BCL2 overexpression in 64 (83%) and BCL6 low expression in 25 (34%). Median 2y-PFS and OS were 71% and 84% respectively. Applying the prognostic score defined in the previous pilot study (risk of 2 points for MYC or BCL2 positivity and 1 point for BCL6 negativity, pooled scores 0-1, 2 and >3) 2y-PFS were different across the 3 groups: 100% *vs* 83% *vs* 64% (p 0.002). While in the pilot study no differences in OS were showed, in this expanded cohort OS were different across the groups: 100% *vs* 89% *vs* 82% (p 0.07). Our data showed that the HIC prognostic score based on MYC, BCL2 and BCL6 expression, outlined in the previous study, was applicable, reproducible and valid in a larger cohort of DLBCL, regardless of MIB1, forecasting significant different PFS and OS rates. This study provides to extend HIC and FISH analysis in a total sample of above 200 cases.