



Dear Friends,

Welcome to the 2021 fall edition of the International Extranodal Lymphoma Study Group (IELSG) Newsletter, which has now a new design.

We are pleased to share with you the highlight of the IELSG studies presented at the last ICML virtual conference (June 2021) and the status of the IELSG trials.

Highlights from 16-ICML

IELSG was able to submit to the 16-ICML five abstracts and all of them were selected for oral presentation.

Intensified (intravenous and intrathecal) CNS prophylaxis in primary testicular diffuse large B-cell lymphoma: 5-year results of the IELSG30 trial (Abstract number 048 – A. Conconi).

Fifty-four patients with untreated stage I or II primary testicular diffuse large B-cell lymphoma (PTL) were treated with R-CHOP21, 53 received at least 3 doses of intrathecal CNS prophylaxis, 48 received at least one dose of iv methotrexate and 50 received prophylactic RT. At a median follow-up of 5 years, 7 patients progressed and 7 died, with 5-year progression-free survival (PFS) of 88% and 5-year overall survival (OS) of 92%. No CNS relapses occurred. Two patients relapsed only at extranodal sites.

Definitive assessment of the primary endpoint will need longer follow-up. Thus far, comparison of these results with those of the IELSG10 trial suggests that combined treatment of PTL with R-CHOP21 plus intensive CNS prophylaxis and loco-regional RT is feasible, may abrogate CNS relapses and lead to very promising outcomes. Nevertheless, late relapses, mainly at extranodal sites, still represent a clinical challenge.

Survey on Primary extranodal follicular lymphoma (IELSG31) (Abstract number 078 – A. Conconi)

IELSG coordinated this international multicenter retrospective survey aimed to describe the clinical features at diagnosis and outcome of a population of extranodal follicular lymphoma (EFL). A dataset, including 608 pathologically reviewed cases from 19 different countries, was analyzed and their outcome was compared to the outcome of a population of nodal follicular lymphomas. Characteristics at diagnosis and clinical course of primary EFL were never extensively described. Skin (n=334), gastrointestinal tract (n=72), 22 of whom with a primary duodenal localization, were the two most frequent presentation sites. These subsets displayed peculiar features at diagnosis and significantly different pattern of survival. After median follow-up of 5.5 years, a superior outcome was observed for primary cutaneous lymphomas and intermediate outcome for primary gastrointestinal lymphomas among whom primary duodenal lymphomas displayed a trend toward the best outcome. All the other primary extranodal sites presented an inferior outcome analogous to the outcome of primary nodal lymphomas. These findings support the hypothesis that some primary lymphoma localizations may represent specific entities.

MATRix induction followed by autologous stem cell transplant or whole-brain irradiation in primary CNS lymphoma. 7-year results of the IELSG32 randomized trial (Abstract number 047 – A.J.M. Ferreri)

The IELSG32 study is an international randomized trial addressing tolerability and efficacy of adding rituximab with or without thiotepa to the high-dose methotrexate and cytarabine combination, followed by a second randomization comparing consolidation with whole brain irradiation (WBRT) or autologous stem cell transplantation (ASCT), in patients with primary CNS lymphoma (PCNSL). MATRix regimen (methotrexate, cytarabine, thiotepa, rituximab) significantly improved outcome of patients with PCNSL enrolled in this trial.

At a median follow-up of 40 months, both WBRT and ASCT resulted in similar PFS rates. Sound assessment of OS, late complications, incidence of secondary tumors, and cognitive impairment require, however, longer follow-up. At 16-ICML, we reported the results of this trial at a median follow-up of 88 months.

HIV-negative patients aged 18-70 years with newly diagnosed PCNSL were randomly assigned to receive 4 courses of methotrexate-cytarabine (arm A), or arm A plus rituximab (arm B), or arm B plus thiotepa (MATRix; arm C). A second randomization allocated patients with responsive/stable disease to WBRT (arm D) or carmustine - thiotepa conditioning followed by ASCT (arm E).

Two-hundred nineteen assessable patients were randomized (arm A 75; B 69; C 75). After induction, 167 had responsive or stable disease; 118 were assigned to WBRT (59) or ASCT (59) while 49 were excluded from second randomization (poor mobilizers, poor conditions and, refusal). Fifteen patients died of toxicity during treatment. Of 87 (40%) relapse-free patients (A 17; B 28; C 42), 14 died (infections, sudden death, cognitive decline, second tumor and car accident). Among 117 patients with relapse, 96 died of lymphoma, 7 died of salvage therapy complications. Eight patients developed second cancers. Neuropsychological tests showed a statistically significant impairment in attentiveness and executive functions in patients treated with WBRT, while transplanted patients had a significant improvement in these functions as well as in memory and quality of life. Patients treated with MATRix (arm C) showed significantly better PFS (7-year: 52% vs 20% for arm A; vs 29% for arm B) and OS rates (7-year: 56% vs 26% for arm A; vs 37% for arm B). No significant difference was seen between the consolidation arms for either PFS (7-year: 55% for arm D vs 50% for arm E) or OS (7-year: 63% vs 57%). Patients treated with MATRix induction and consolidation had a 7-year OS of 70%, without a significant difference between WBRT and ASCT.

In conclusion, the MATRix regimen was associated with an excellent long-term outcome. WBRT and ASCT had comparable efficacy. MATRix and ASCT did not result in higher non-relapse mortality or second tumors incidence in comparison to the other study arms, whereas WBRT led to impairment of specific cognitive functions.

Impact of different induction regimens on the outcome of primary mediastinal B-cell lymphoma in the prospective IELSG37 trial (Abstract number 049 – M. Martelli)

Patients with newly diagnosed PMBCL were eligible. Initial therapy was based on a combination containing rituximab and anthracyclines. The regimen was chosen according to local practice. Upon central review of post-induction PET scans, responding patients were randomized to observation versus consolidative RT. Responses were defined according to the Lugano classification using the Deauville 5-point scale (DS). Patients progressing during induction did not have central PET review and in the present analysis were assigned DS score 5.

Five-hundred forty-five patients (209 men, 336 women) were enrolled and treated. The rate of complete metabolic responses (CR, defined by DS 1- 3) did not differ significantly across regimens, however an unbalanced distribution of DS score was evident, apparently due to the rate of patients with a probable induction failure (DS5) more than 2 times higher for CHOP21 in comparison to the other regimens. At preliminary analysis, there was no significant association of advanced stage, older age, extranodal infiltration, poor performance status, bulky disease, unfavorable international prognostic index (IPI) and larger metabolic tumor volume with the use of CHOP21. Patients receiving DA-EPOCH-R were somehow younger than the rest. In conclusion, initial regimen may have critical impact on PMBCL outcome. R-CHOP21 appeared inferior to dose-dense/dose-intensive regimens.

Phase II trial of rituximab plus chlorambucil followed by a 2-year subcutaneous rituximab maintenance in MALT lymphoma patients (IELSG38) (Abstract number 079 – M.C. Piroso)

This study aims to evaluate the role of rituximab maintenance in mucosa associated lymphoid tissue (MALT) lymphoma patients after the administration of a front-line rituximab-chlorambucil regimen. In a prior study (IELSG19), this regimen, without maintenance, produced superior event-free (EFS) and PFS in comparison to either agent alone. Patients with complete (CR), partial response (PR) or stable disease were eligible for maintenance with subcutaneous rituximab every two months for two years. The study enrolled 112 patients, 53 women and 59 men (median age 65 years; range 32-86). Primary lymphoma localization was gastric in

32% and non-gastric in 68% of Patients. Over half of patients had advanced disease. MALT IPI showed low risk in 29%, intermediate risk in 40% and high risk in 30%.

Twenty-four patients did not complete study treatment. Fifteen ceased before maintenance and nine discontinued during maintenance. Best response was CR in 87% of patients. In the intention-to-treat population, CR rate increased over time from 53% at the end of induction to 65% at the end of maintenance. The IELSG38 is the first trial that specifically evaluated subcutaneous rituximab maintenance in patients with MALT lymphoma. No new safety signals were identified. Long-term disease control was achieved in the majority of patients and, despite the inclusion of more high-risk patients, the 5-year PFS compared favorably with the IELSG19 trial.

Ongoing prospective clinical studies

IELSG47 – Phase II study of combination of ibrutinib and rituximab in untreated marginal zone lymphomas (MZL) (MALIBU)

The aim of the study is to assess the safety and efficacy of the combination of rituximab and ibrutinib in extranodal MZL patients and to explore its activity in splenic MZL (30) and nodal MZL (15) as exploratory subset.

 112
Patients recruited

 130 EMZL
Evaluable patients to recruit

 Open in
IT, CH, FR, BE, PT

IELSG45 – Randomized phase II trial on fitness- and comorbidity- tailored treatment in elderly patients with newly diagnosed primary CNS lymphoma (FIORELLA)

This study involves patients aged ≥ 70 years. The more fit patients (Part A) will receive the standard chemotherapy combination (high-dose methotrexate, procarbazine and rituximab) as induction. Responding patients will receive either procarbazine or lenalidomide as maintenance therapy; the aim is to compare the efficacy of these two drugs. The more fragile patients (Part B) will receive a less aggressive therapy consisting of concomitant whole-brain radiotherapy, temozolomide and rituximab as induction therapy, followed by temozolomide as maintenance treatment; the aim is to evaluate the efficacy of this combination of treatment. Due to some issues arisen during the conduction of the trial, an amendment will be implemented soon.

 59
Patients recruited

 UNDER EVALUATION
Evaluable patients to recruit

 Open in
IT, CH, DK, FI, IL

IELSG49 – Phase II trial of acalabrutinib in combination with tafasitamab in patients with previously treated marginal zone lymphomas (MZL)

This study will determine the efficacy of tafasitamab in combination with acalabrutinib in patients with relapsed or refractory MZL.

 1
Patients recruited

 24
Evaluable patients to recruit

 Open in
IT, CH

Ongoing retrospective clinical studies

IELSG44 – FDG-PET evaluation for marginal zone lymphoma and its prognostic role: an international multicenter retrospective analysis (PIMENTO)

The IELSG44 PIMENTO study is a multicenter retrospective analysis that will assess the role of PET for the staging and for the assessment of response and outcome prediction in MZL.

 148
Patients recruited

 350
Evaluable patients to recruit

 Open in
IT, CH, FR

Studies in their follow-up phase

Several studies (IELSG30, IELSG32, IELSG37, IELSG38, IELSG39, IELSG40, IELSG42 and IELSG43) are now in their follow-up phase. Since for some of them it is time to start the data analysis, it is of paramount importance to have **up-to-date data in the database**. Please check with your personnel or with the specific IELSG clinical project manager if the data of your site are complete for all the recruited patients. Queries can come from our coordination center. For other, we are actively working on manuscript preparation.

Prospective trials in the pipeline

IELSG48 (randomized study of BTKi ± Rituximab in untreated SMZL)

No randomized trials have been conducted in SMZL and, as consequence, there is no consensus on treatment for newly diagnosed patients. At present, splenectomy has been replaced largely by rituximab monotherapy, which is the guideline recommended medical approach in SMZL. However, rituximab is not registered for this indication, thus limiting accessibility to this agent for SMZL patients. Since the NF-κB pathway is pervasively mutated and constitutively activated in SMZL, the IELSG designed this study aimed at testing the hypothesis that a chemotherapy-free combination of rituximab and a BTKi can be superior to the standard of care rituximab monotherapy in previously untreated, symptomatic patients with SMZL. If positive, the study will be practice changing and will provide evidence supporting first line treatment with a chemotherapy free regimen. The study will also provide prospective validation of the IELSG46 study results, in a modern setting where splenectomy is no longer required for diagnosis. The primary endpoint is PFS at 3 years, OS and remission rates are secondary endpoints. An exploratory endpoint is to study by profiling baseline liquid biopsy treatment effect on biomarker subgroups according to IELSG46 criteria.

IELSG50 (Pembrolizumab and radiotherapy for previously untreated patients with limited stage NK/T cell lymphoma who are not eligible to chemotherapy)

The full dossier of the study has been submitted to the Chinese Authorities. The site initiation visit for the Shanghai site is planned in January 2022.



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