INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

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NEWSLETTER 25

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Dear all

More than two months have already elapsed since the 10th Anniversary Meeting we had in Lugano in February. We want again to thank all of you who participated to the meeting and contributed to its success.
Here we want to remind you the principal decisions taken by the assembly at the end of the meeting.

Some **retrospective studies** concerning **extranodal follicular lymphomas** and **primary bone marrow lymphomas** will be launched and protocols are in preparation.

Enclosed you can find a **report concerning our 10th annual meeting** that will be published in the bulletin of the Swiss Cancer Research Organizations (SAKK Bulletin, SKBVCS 27 nr. 2/07).

IELSG presentation at the next **EHA meeting in Wien**:
Our abstract on the **IELSG 23** study (**head and neck lymphoma**) results has been accepted for an **oral communication** and the abstract concerned the **IELSG 14** study of **bone lymphoma** has been accepted for a **poster presentation**. The text of the abstracts is available online at http://www.ielsg.org/publicfr.html.

We are also happy to inform all of you that following papers have been accepted for publication:

M. Ponzoni, F. Berger, C. Chassagne-Clement, M. Tinguely, A. Jouvet, J.M. Ferreri, S. Dell'Oro, M.R. Terreni, C. Doglioni, J. Weis, M. Cerati, M. Milani, P. Iuzzolino, T. Motta, A. Carbone, E. Pedrinis, J. Sanchez, J-Y. Blay, M. Reni, A. Conconi, F. Bertoni, E. Zucca, F. Cavalli and B. Borisch. **Reactive perivascular T-cell infiltrate predicts survival in primary CNS B-cell lymphomas.** Submitted to **British Journal of Haematology**.

J. M. Ferreri, G. P. Dognini, E. Campo, R. Willemze, J. F. Seymour, O. Bairey, M. Martelli, A. De Renzo, C. Doglioni, C. Montalbán, A. Tedeschi, A. Pavlovsky, S. Morgan, L. Uziel, M. Ferracci, S. Ascani, U. Gianelli, C. Patriarca, F. Facchetti, A. Dalla Libera, B. Pertoldi, B. Horvath, A. Szomor, E. Zucca, F. Cavalli, and M. Ponzoni. **Variations in clinical presentation, frequency of haemophagocytosis and clinical behavior of intravascular lymphoma diagnosed in different geographical regions.** Submitted to **Haematologica**.

M. Ponzoni, A. J. M. Ferreri, E. Campo, F. Facchetti, L. Mazzucchelli, T. Yoshino, T. Murase, S. A. Pileri, C. Doglioni, E. Zucca, F. Cavalli, and S. Nakamura **Definition, diagnosis and management of intravascular lymphoma: proposals and perspectives from an international consensus meeting (Locarno, Switzerland; December 9-10, 2005)** Submitted to **Journal of Clinical Oncology**.

Last but not least, we want to remind you that the following studies are open for accrual:

IELSG 19
Multicenter randomized trial of chlorambucil versus chlorambucil plus rituximab versus rituximab alone in extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)

IELSG 20
Randomized phase II trial on primary chemotherapy with high-dose methotrexate, alone or associated with high-dose cytarabine, followed by response- and age-tailored radiotherapy for immunocompetent patients with newly diagnosed primary central nervous system lymphoma

IELSG 24
A phase I study of intrathecal rituximab in patients with lymphomatous meningitis

IELSG 25A
Phase II Study of VELCADE™ in patients with extranodal marginal zone B-cell lymphoma of MALT-type pretreated with one prior systemic therapy regimen

IELSG 25 B
Phase II Study of VELCADE™ in patients with extranodal marginal zone B-cell lymphoma of MALT-type pretreated with more than one prior systemic therapy regimen

IELSG 26
A clinico-pathologic study of Primary Mediastinal B-cell lymphoma

IELSG 27
A Clinico-pathological phase II study with translational elements to investigate the possible infective causes of non-hodgkin lymphoma of the ocular adnexae with particular reference to Chlamydia species and the effects of MALT lymphoma treatment with tetracycline

IELSG 28
A retrosoective international study of primary extranodal marginal zone lymphoma of the lung (BALT-lymphoma)

Further information are available at the website www.ielsg.org.

Best wishes,

F. Cavalli, E. Zucca, A. Conconi, C. Morinini, M. Bertini

Highlights from the 10th Annual Meeting of the International Extranodal Lymphoma Study Group (IELSG) Investigators

Volmar Belisario-Filho, Oncology Institute of Southern Switzerland, Bellinzona

The continuous contribution of different international Institutions during the last ten years, has allowed to improve our knowledge on the biology and therapy of the extranodal lymphomas. The 10th annual meeting of the IELSG has been held in Lugano on February 9-10, 2007, with the participation of approximately one hundred people from different countries. The discussion of the ongoing studies of the group and the planning of the future ones, were the aim of the meeting. Here we present a summary of the main topics addressed.

Ongoing IELSG clinical studies

IELSG 19 «Multicenter randomized trial of chlorambucil versus chlorambucil plus rituximab versus rituximab alone in extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)»
The aim of the IELSG 19 study initially was to assess the therapeutic activity and safety of the combination of Chlorambucil and Rituximab in MALT lymphomas and to determine whether the addition of Rituximab to Chlorambucil will improve the outcome of MALT lymphoma in comparison to treatment with Chlorambucil alone.
All the MALT lymphoma patients with localised disease at any site who do not respond to local therapy, the H.pylori-negative gastric lymphomas or those who failed antibiotic therapy are eligible as well as those with disseminated or multifocal MALT lymphoma at any extranodal site. Because of the excellent and fast recruitment, after the accrual of 250 patients, in April 2006, an amendment was introduced to add a third arm with rituximab alone and in the fourth trimester of 2006 the study was open again in Italy, Switzerland and France. Thirty-four patients have entered the study after the addition of the Rituximab arm. Patients are randomized among chlorambucil alone, chlorambucil plus rituximab and rituximab alone with an allocation ratio of 1 : 1 : 6. Therefore, the recruitment of further 200 patients is required in order to achieve a total enrolment of approximately 450 patients which, with an assumed adjustment of 10% for non-evaluable patients, will allow the analysis of approximately 130 patients for each trial arm. With this design the study will be powered to compare each of the 2 experimental arms against chlorambucil alone. The analysis of chlorambucil vs chlorambucil + rituximab in the first 250 patients will be reported first and another analysis will be done later with the rituximab arm and the updated results of the 2 first arms. The recruitment of all study patients will have to be completed before any report. Pathologic review is planned for all the patients included in the study and is ongoing.

IELSG 20 «Randomized phase II trial on chemotherapy with high-dose methotrexate, alone or associated with high-dose cytarabine, followed by response-and age-tailored radiotherapy for immunocompetent patients with newly diagnosed primary CNS lymphoma»
This is a multicentre open label randomized phase II trial, aimed to compare the antitumor activity of the sole high-dose methotrexate with the combination of high-dose methotrexate and high-dose cytarabine as primary chemotherapy (max. four courses). In both study arms, at the end of the chemotherapy program, responding patients will undergo CNS radiotherapy but in patients older than 60 years this radiotherapy will be at investigator's discretion. According to the early stopping rules of the study protocol, an interim analysis of response was done after the randomization of 40 patients and the results were submitted to an independent review board (3 expert investigators with experience and a strong publication record in hemato-oncology or neuro-oncology). The review board advice was to continue the study and 56 patients were enrolled thus far. The accrual should be hopefully completed within 18 months.

IELSG 26 «Clinico-pathological study of primary mediastinal B cell lymphoma»
The WHO classification recognises primary mediastinal B-cell lymphoma (PMBL) as a distinct entity. The pathobiology of PMBL has been widely studied but it is still debated up to now. The optimum chemotherapy schedule is unclear. Although randomised studies have not shown a significant difference between CHOP and more dose-dense third generation regimens such as MACOP-B in DLBL, the retrospective study in PMBL by the IELSG suggested that outcomes were better in patients treated with dose-dense regimens by comparison with conventional CHOP. The inclusion of Rituximab as part of initial CHOP–like therapy for PMBL has clearly improved response rates and overall survival in two recent prospective phase II trials. The role of mediastinal radiotherapy is also unclear. Retrospective series suggest that the best outcomes are seen where consolidation radiotherapy is given to the mediastinum, particularly among the large proportion of patients with residual masses at the completion of chemotherapy. However, there are still large numbers of patients cured by chemotherapy alone in other series, and the long-term toxicity of irradiation, particularly the risks of second malignancy, should be avoided if possible. Once again, the effect of adding Rituximab to the chemotherapy may alter the utility of subsequent irradiation. Studies of functional imaging using either Gallium scans or Positron Emission Tomography (PET) have suggested that it may be possible to distinguish residual mediastinal masses which contain active lymphoma from those in which the lymphoma has already been cured and only sclerotic material remains. PET studies performed to date are not conclusive, and specifically the negative predictive value is not yet high enough for many clinicians to omit radiotherapy solely on the basis of a negative PET scan. On these bases the IELSG-26 prospective multi-centre study has been designed to investigate in an homogeneous group of PMBL the pathobiology and prognostic utility of PET scan. Patients will be enrolled on the basis of the clinical and pathologic characteristics of their lymphoma. Central review of all pathology will be carried out, with storage of fresh frozen biopsy material wherever possible. PET scans will be performed at the start of chemotherapy and at its conclusion, with central review of the images for quality control. Patients will receive one of the standard chemo-immunotherapy protocols currently in use for diffuse large B-cell lymphoma (i.e., R-CHOP-21, R-CHOP-14,R-MACOP-B, R-VACOP-B, R-ACVBP). Consolidation radiotherapy to the mediastinum will be carried out according to the local protocol of the treating centre.

IELSG 27 «A phase II study with translational elements of antibiotic therapy in newly diagnosed ocular adnexal lymphomas (OAL) of MALT-type»
The possibility that OAL (lachrymal gland, conjunctiva and orbital soft tissue) arise in the context of a chronic inflammation has been suggested, however, the source of the involved antigen(s) remains to be clarified. *Chlamydia psittaci* DNA has been detected in 80% of Italian patients with OAL. *Ch. psittaci* is the etiologic agent of psittacosis, a human infection caused by exposure to infected birds, cats and other pets. This microorganism is an obligate intracellular bacterium growing in eukariotic cells, and has a tendency to cause persistent infections. In particular, *Ch. psittaci*-associated follicular conjunctivitis may favor the development of OAL through a chronic antigenic stimulation. Analogous to gastric lymphomas, where Helicobacter pylori eradication is a well established therapeutic strategy, eradication of *Ch. psittaci* infection with a specific antibiotic therapy may constitute an attractive, novel therapeutic approach for OAL. A recent trial provided evidence for an antibiotic treatment with doxycycline as a novel active strategy in some OAL showing objective lymphoma response in half of the patients. Tumor response was observed even in relapsing and previously irradiated patients, and in patients with lymph nodes involvement. These observations require confirmation in an open, non-randomized phase II trial. Under the sponsorship of the IELSG, sufficient patients with OAL (*chlamydia* positive and negative) will be recruited to this study so that 29 chlamydia-positive patients with newly diagnosed stage-IE, OAL of MALT-type will be treated with doxycycline 100 mg, bid orally, for 3 weeks. The primary endpoint of the trial is the objective lymphoma response rate following *Ch. psittaci*-eradication as assessed by MR imaging. The *Ch. psittaci*-eradication rate following antibiotic therapy, the time to best lymphoma response and the objective response duration will be the secondary endpoints. The presence of other infectious agents (herpes simplex virus, EBV, adenoviruses, and *H. pylori*) will be also explored as well as the presence of chromosomal alterations.

IELSG 28 «Retrospective study of BALT lymphoma»
Bronchus mucosa-associated lymphoid tissue (BALT) Lymphoma is a rare entity. Aim of this study is to improve our understanding of lung lymphoma of MALT type. Histological, immunophenotypic, cytogenetic and molecular characteristics will be analysed to find if there's any link between pathological patterns, clinical characteristics and the clinical outcome. This will require the availability of tumor specimens (paraffin blocks) from all the patients with BALT lymphoma for whom complete clinical information about diagnostic procedure and treatment outcome are available.

The educational session

Once again, relevant scientific topics have been addressed by international experts in the educational lectures of the 10th IELSG meeting.

Stefano A. Pileri from the University of Bologna, Italy, addressed their work on the gene expression profile of the Peripheral T-cell lymphoma unspecified (PTCL/U), the most com-

mon form of PTCL. They could demonstrate that PTCLs/U have a distinct gene expression pattern, most closely related to activated peripheral T-lymphocytes (HLA-DR+), either CD4+ or CD8+. When compared with normal T-cells, PTCLs/U display deregulation of functional programs often involved in tumorigenesis (e.g. apoptosis, proliferation, cell adhesion, and matrix remodeling). Products of deregulated genes can be detected in PTCLs/U by immunohistochemistry. Among others, PTCLs/U aberrantly express PDGFRa, a tyrosine-kinase receptor, whose deregulation is often related to a malignant phenotype. Notably, both phosphorylation of PDGFRa and sensitivity of cultured PTCL cells to imatinib (as well as to an inhibitor of histone-deacetylase) were found. These results, which might be extended to other rarer PTCL categories, may have relevant implications for tumor pathogenesis and clinical management.

Paolo Boffetta from the International Agency for Research on Cancer, Lyon, France, discussed about the epidemiological aspects of non-Hodgkin's lymphoma (NHL), focused on the stable incidence rate from the late 1990s, explained in part by the improvement in diagnostic procedures and management specially in HIV (non AIDS) infected people. Altered immunological function, either immunostimulation or immunosuppression, continue to carry an increased risk of NHL. For example, immunosuppressed renal transplant patients have a risk 30 times higher for developing lymphoma compared to the general population. The association of a chronic infection with lymphoma pathogenesis was also discussed, with a particular attention to the role of HCV. The environmental and occupational factors, as well the familial risk, may also have a possible role to the pathogenesis of NHL. Future studies should consider risk factors for specific subtypes of NHL, incorporate biological markers of exposure and consider gene-environment interactions. Large series of patients need to be included in such studies, which can be best achieved within the framework of international collaborations.

James O. Armitage, from the University of Nebraska, presented the recent advances in the treatment of patients with non-Hodgkin's lymphoma with emphasis to the in vivo chemotherapy sensitivity testing, personalized medicine, and developing standard treatments for rare diseases (e.g. peripheral T-cell lymphoma). A recent possibility of doing in vivo chemotherapy sensitivity testing is the use of PET during and after the lymphoma's treatment. Recent data show that early PET scans might identify those patients whose tumors are particularly sensitive to a chemotherapy regimen so it can be continued, or those who are not going to be cured with a standard regimen so the treatment could be changed. Several studies are ongoing to better clarify this issue. A list of new drugs, including lenalidomide, bortezomib, pralatrexate, vorinostat, and romidepsin, have shown to be promising in B and T-cell lymphomas. The peripheral T-cell lymphomas are raising a continuous and increasing interest from scientific community because of the urgent need to identify new specific treatment modalities. Genetic and proteomic studies will hopefully help to identify the targets for the development of new therapies with the possible application of a personalized-medicine approach.

Antonio Lanzavecchia from the Institute for Research in Biomedicine, Bellinzona, Switzerland, presented their work on the study of the function, generation and maintenance of T-cells subsets. In the secondary lymphoid organs, under antigenic stimulation, naive T lymphocytes interact with antigen-presenting dendritic cells and are clonally expanded generating large numbers of effector cells that migrate to non-lymphoid tissues where they fight pathogens. A small fraction of primed T cells persist for years as memory cells. Naive, effector and memory T cells have different homing capacity that is regulated at the level of expression of lectins, integrins and chemokine receptors. CD4+ and CD8+ memory T cells can be divided in two distinct subsets depending on their homing capacity and immediate effector function: i) central memory T cells (TCM) expressing the lymph node homing receptors CCR7 and CD62L and incapable of immediate effector function and ii) effector memory T cells (TEM) lacking CCR7, expressing receptors to migrate into inflamed non-lymphoid tissues and endowed with the capacity to rapidly produce inflammatory cytokines such as IFN-g and IL-4. Thus, while TEM represent fully polarized effector T cells (Th1, Th2 or CTL) and can confer immediate protection against a second encounter with the same pathogen, TCM represent non-effector lymph node homing T cells that can rapidly mount a secondary response generating large numbers of effector cells. The strength of stimulation regulates T cell progression through thresholds of proliferation, differentiation and death. Memory T cells could be maintained by either persisting antigen or by cytokines like IL-7 and IL-15. Importantly, in response to cytokines TCM divide asymmetrically maintaining their number and, at the same time, differentiating to TEM-like cells acquiring effector function and switching chemokine receptor expression from CCR7 to CCR5. Thus, TCM may function as «memory stem cells» under homeostatic conditions.

Future studies

The IELSG assembly has also decided to set up novel retrospective surveys to study the primary extranodal follicular lymphomas and the primary bone-marrow lymphomas.

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