MINUTES

ELI's 3rd Conference on :

Follicular Lymphoma and Transformation at the Rituximab era

Date and place: Hotel AC Atocha, Madrid

25-26 February 2015

Participants: Miguel Alcoceba (ES), Sara Alonso (ES), Marc André (BE), Kirit Ardeshna (UK), Reyes Arranz Saez (ES), Oscar Blanco (ES), Luana Conte (IT), Rita Countinho (PT), Riccardo Dalla-Favera (USA), Andrew Davies (UK), Laurianne Drieu La Rochelle (FR), Jehan Dupuis (FR), Marion Fournier (FR), Juan Fernando Garcia (ES), Alejandro Martin Garcia-Sancho (ES), Philippe Gaulard (FR), Marcos Gonzalez Diaz (ES), Carlos Grande Garcia (ES), Anton Hagenbeek (NL), Corinne Haioun (FR), Susannah Howlett (USA), Andrea Janikova (CZ), Camille Laurent (FR), Sandra Lockmer (SW), Andres Lopez (ES), Armando Lopez-Guillermo (ES), Stefano Luminari (IT), Laura Carola Magnano (ES), Santiago Mercadal Vilchez (ES), Carlos Montalban (ES), Santiago Montes-Moreno (ES), Francisco Javier Peñalver (ES), Alessandro Pulsoni (IT), Giuseppe Rossi (IT), Antonio Salar (ES), Véronique Staniek (FR), Luc Xerri (FR), Emanuele Zucca (SW).

ELI Members: Igor Aurer (ZR), André Bosly (BE), Dolores Caballero (ES), Bertrand Coiffier (FR), Pascal Deschaseaux (FR), Martin Dreyling (GE), Massimo Federico (IT), Maria Gomes da Silva (PT), Eva Kimby (SW), Hervé Tilly (FR), Marek Trneny (CZ) – Claire Morin (FR).

Minutes:

WEDNESDAY, FEBRUARY 25TH 2015

The meeting started at 2:00pm with an introduction from Massimo Federico and Dolores Caballero, co-chairs. During the afternoon, 3 sessions followed each other:

- Session 1 – Overview of Transformation:

Andrew Davies replaced Silvia Montoto and gave a presentation on "Clinical Transformation". His slides showed that the impact of initial therapy (treatment of FL) is uncertain but that the outcomes (OS) are much better if the patient receive Rituximab.

Kirit Ardeshna then presented the "Risk of transformation in advanced, low tumor burden diseases". Based on GELF and NCRI criteria, evidence from pre- and post- rituximab eras suggests that deferring therapy does not increase risk of transformation.

Santiago Montes-Moreno presented the main histopathological aspects of transformation which he defined by the acquisition of a distinct phenotype by the neoplastic clone:

- DLBCLs with/ without concurrent MYC and BCL2 translocations are the most common phenotype in the transformation Phenotype variations related to genetic events (MYC, BCL2, p16, p53) and CD30 expression should be routinely identified by IHQ. FISH analysis is also required to identify genetic alterations in MYC, BCL2 and BCL6.

Riccardo Dalla-Favera concluded the session with a lecture on "Genetic aspects".
His models of clonal evolution to t-FL showed 2 pathways: linear and divergent.
There are shared and unique genomic lesions in FL and t-FL. He presented first the "Genetic lesions acquired early in the common mutated precursor": CREBBP (CREB binding protein) in the BCL6/p53 network and Mll2. Then "Genetic lesions at transformation": β2-microglobuline.
This led to 3 points:

- What is the history of clonal evolution during transformation?
  Mostly divergent evolution pattern
- What are the molecular determinants of FL transformation?
  Shared: chromatin modification and apoptosis
  tFL-specific: cell cycle, proliferation, DNA damage response
- Is tFL a distinct entity from *de novo* DLBCL?
  More similar to GCB-DLBCL, but unique genetic profile

In conclusion, therapeutic approaches should be aimed at eradicating the precursor cell early at diagnosis.

- Session 2 – Prognosis of Transformation (Lymphoma groups)

LYSA – Hervé Tilly based his presentation on the PRIMA study on 3 axes:

- Incidence of histological transformation
  - 194 patients (with a biopsy at 1st relapse): 40% showed transformation (1,5% per year).
  - Median time to FL relapse: 23 months, to T: 10 months
- Risk factors and treatment options
  - Impact of some factors, no impact of therapy (trend for maintenance)
- Outcome with transformation
  - OS poorer with T
  - Patients with ASCT have a better survival
  - OS of transformed patients is similar to relapse DLBCL

FIL – Massimo Federico based his presentation on FIL experience.

- FIL Survey: 234 patients in 8 centers, OS of t-FL: 75% at 5 years / OS of DLBCL: 72%
- FOLL05 study: 181 patients and 71 with new biopsy => 7 pts (10% of biopsied, 4% of relapses, 2% of all cases) with T, 6 DLBCL, 1 Burkitt.
  Cumulative risk at 5 years 4.4% among those relapsed, and 11.6% if we consider only the 71 pts with a re-biopsy

GELTAMO – Armando López-Guillermo presented the retrospective assessment of histological T in FL in several studies from the Spanish Groups.

- Spanish studies:
  - Risk of transformation: 7% at 5 yrs, 10% at 10 yrs
  - Age>60, FLIPI high and no previous Rituximab Treatment are prognostic factors
  - OS from T ; 56% at 1 yr, 32% at 5 yrs
  - Patients with ASCT do better
- Hospital Clinic, Barcelona, cohort:
  - DLBCL vs t-FL: prognosis for de novo DLBCL is better than t-FL (CR, PFS and OS) but gets worse for relapsed DLBCL.
- Discussion on patients with “composite” t-FL/DLBCL lymphoma

SAAK – Emanuele Zucca noticed that only patients treated with Rituximab were kept in the study, which doesn’t left enough cases for this presentation.

NLG – Sandra Lockmer presented the Nordic Lymphoma Group results on behalf of Eva Kimby. Those data (from the Swedish Lymphoma Registry) are organized in 3 periods: pre-Rituximab/transitional/established Rituximab with patients diagnosed with FL between 2000 and 2012.

The discussion raised the question of difference between t-FL and relapsed DLBCL. The plateau seen after 5-10 years might be related to the limited follow-up on patients after some years. There is thus a need of prospective studies to better understand the long-term evolution of the FL patients.

Another issue is the differentiation between second transformation and relapse which could get easier with systematic re-biopsy.

It is also essential to collect and share data from ELI's groups and centres. It could be interesting to set up a meta-analyse on the prospective studies.

A comment is made on the GCB type of FL (ABC lymphomas are others).

- Session 3 – Prognostic markers of transformation

Prognosis – Stefano Luminari introduced his presentation with a comment on pre-Rituximab studies and the lack of recent and dedicated studies to transformation.
A post-Rituximab study from the Mayo Clinic shows that only time to t-FL was prognostic.
If the interest of a retrospective study to investigate clincal prognostic features of t-FL is confirmed, he then recommended joining efforts and looking back to the clinical, pathologic and genetic data in the biopsy-proven t-FL patients.

PET – Jehan Dupuis addressed the question of PET as a non-invasive method to detect transformation. The optimal SUV cutoff is difficult to determine between low-grade FL and t-FL but SUV max<11,7 is almost always associated with indolent histology, whereas SUV max>17 is almost always associated with transformation. He concluded on the importance on targeted biopsy to characterise transformation as well.

Suspecting t-FL? – Luc Xerri presented the controversial predictive value of CD68+ macrophages as well as PD1+ TFH cells and FOXP3+ Tregs. However, CD163+ macrophages have predictive value, but opposite effect according to therapy! (PRIMA trial vs. Vancouver cohort). In conclusion, histopathological prognostication in FL is highly dependent on treatment.

The discussion focused on the interest of PET at relapse.

THURSDAY FEBRUARY 26TH

- Session 4 – Treatment of transformed follicular lymphoma

First line therapy – Martin Dreyling started his presentation with a question about 3B lymphomas – which are DLBCL according to Philippe Gaulard – while 3A subtype is considered as FL. His talk showed that:

- R-CHOP seems to be superior to alkylating agents only
- The benefit of ASCT depends on chemo (before or at relapse)

Salvage therapy – Anna Sureda finally could not attend the Workshop.

- Discussion on future project

Massimo Federico showed some data about what could be a common project for ELI members. First, everyone agree on the interest of biopsy to every case of t-FL. He then noticed than only 50% of transformations occurs at 1st relapse, and studies must include patients followed from initial diagnosis of FL and not just at transformation.

The first aim of such a project would be to define criteria for diagnosis of t-FL and assess the risk of transformation. The primary objectives would be to assess the risk of transformation (D. Caballero) for patients with FL treated with R-Chemo. The secondary end-point could be the identification of a R-FLIPI prognostic score for t-FL (S. Luminari).

Retrospective project: updating data from at least 7 studies (4700 cases) + more cases to be provided from other studies or registries
Prospective study: as FL treatment is moving forward (R2), it might be better pursuing collaboration on new trials.

Dolores Caballero presented a possible biological project to develop between ELI centers. She would include the validation of biological data from previous retrospective studies in a prospective study, together with genetic and clonality studies of samples at diagnosis and at transformation. Other objectives would include the development of studies trying to analyse the activity of new molecules on transformed and follicular cell lines – biological studies by NGS, miRNA and CNV.

In conclusion all attendants agreed on the following proposition:

A 3 month-credit is required to write a protocol by a provisional Steering Committee composed by Massimo Federico, Dolores Caballero, Gilles Salles, Martin Dreyling, Kirit Ardeshna, Marek Trneny, Maria Gomez da Silva and Bertrand Coiffier, . The protocol will then circulate among ELI members and presented for approval during the Lugano Conference

Next meeting is scheduled during next ICML in Lugano.
Wednesday, JUNE 17 room C (40 px theater style) from 07:30 to 13:00