Novità dall’EHA >> [ Leucemie acute linfoidi ]

ALL

Relatore: R. FOÀ

27-28 ottobre 2008
Borgo S. Luigi – Monteriggioni (Siena)
ARGOMENTI SELEZIONATI

- Biologia
- Particolare interesse nelle LAL-T
- Terapia
1. **Unique activating mutations of JAK2 in the acute lymphoblastic leukemias of Down syndrome - Biological and therapeutic applications. S Izraeli, Ramat Gan**
   - DS children have an increased risk of AMKL and ALL.
   - Acquired JAK2 mutations found in 18% of ALL.
   - Potential role of JAK2 inhibitors in this distinct subgroup.

2. **Time to leukemia (TTL) assessed in NOD/SCID mice transplanted with primary ALL leukemia cells determines early relapse in patients and is identified by a specific gene signature. H. Meyer, Ulm**
   - Blasts from 50 childhood ALL transplanted in N/S mice.
   - TTL growth <10 wks in 6 cases vs 44 with >10 wks.
   - Median survival 6 cases 13.1 ms vs 50.7 mo for 44 cases.
   - Different GEP between two groups (confirmed by PCR).
3. Identification of cancer stem cells in B-cell lymphoid hematologic malignancies. HN Nishida, Tokyo

- Stem cell properties of B-ALL cell lines and primary pediatric pre-B ALL samples evaluated in vitro and in vivo.
- Small subpopulations of CD9+/high cells in cell lines shown to have stem cell characteristics within the clone in vitro and in vivo.
- Mice injected with CD9+ cells died of leukemia within 30-40 days, while those injected with CD9- cells survived.
- CD9+ cells were found also in PB or BM of primary ALL samples and showed a significant correlation with CD34 expression in many cases.
- CD9+ express by GEP stem cell-associated genes.
1. Treatment of adults with newly diagnosed ALL with multiple doses of intravenous pegylated asparaginase in an intensified pediatric regimen. P. Srivastava, Los Angeles

- **Aim**: Assess feasibility of using an intensive pediatric regimen containing multiple doses of PEG-ASP in adults with newly-diagnosed ALL

- **Results**: Administration of multiple doses of PEG-ASP IV to adults (ages 19-57 years) in an intensified BFM-based pediatric-like strategy is feasible and provides long term asparagine depletion.
2. Short-course Imatinib added to chemotherapy improves early but not long-term outcome in adult Ph/Bcr-Abl ALL: 5-year follow-up results of study NILG-09. R. Bassan, Bergamo

- 2000-06: 33 Ph+ pts treated with chemo + intermittent IM courses vs 35 with chemo alone.
- CR 30/33: 91% vs 80%, NR 1 vs 6, ED 2 vs 1.
- Ability to perform a SCT increased from 43% to 67%.
- No apparent improvement on molecular monitoring.

3. Dasatinib monotherapy as 1st line treatment of Ph ALL patients: Update of the GIMEMA LAL1205 study. R. Foà, Roma
Dasatinib 70 mg twice a day (total planned treatment is 12 weeks, i.e. 84 days)

Diagnostic work-up (within 7 d) and immunophenotypic & molecular monitoring of MRD carried out centrally in Rome
INTERIM ANALYSIS OF RESPONSE

- Response to 7-day PRD pre-phase: 24 patients (82.76%) ≥75%, 5 patients (17.24%) <75%
- Hematological CR (HCR): **34/34 of evaluable patients (100%)**
  - 32 pts (94.12%): HCR at 1\textsuperscript{st} determination (d +22)
  - 1 pt (2.94%): HCR at 2\textsuperscript{nd} determination (d +43)
  - 1 pt (2.94%): HCR at 3\textsuperscript{rd} determination (d +57)
- No fatalities during treatment
- In 10 patients, at least 1 SAE, for a total of 23 SAEs
- Overall good compliance (only 1 pt stopped treatment)
INTERIM ANALYSIS OF GIMEMA LAL1205. CONCLUSIONS I

- Feasible with overall good compliance, also in old(er) patients
- No deaths
- Together with Imatinib protocol for patients >60 yrs, over 70 Ph+ ALL treated with a TK inhibitor alone as 1st line treatment with no deaths in induction
- 100% HCR, with early HCR achievement in most patients (94.12%)
- Marked and rapid debulking of disease documented by immunophenotypic and molecular monitoring
- Evidence of immunophenotypic and molecular negativity
### CONCLUSIONS OF INTERIM ANALYSIS OF GIMEMA LAL1205. II

- Degree of PCR response of prognostic relevance
- Greater sensitivity of p190+ cases
- Post-CR treatment not part of the present study and the most relevant open question (age, biologic response, etc)
- So far, 9 relapses (all relapses after the induction phase): 6/9 relapses on TK inhibitors alone
- Role of mutations at presentation, on MRD+ cells, at relapse on 6 relapsed patients: 3 T315I, 1 E255K, 2 wt
3. Prior treatment with novel tyrosine kinase inhibitors allows stem-cell transplantation (SCT) in a less advanced disease phase and does not increase SCT toxicity in patients with CML and Ph ALL. A. Shimoni, Tel Hashomer

- Prior TKI treatment allows SCT in a less advanced disease phase in a large subset of patients and does not increase the incidence of treatment-related organ toxicity, engraftment failure or GVHD. nTKI treatment is a safe and effective salvage therapy for patients failing imatinib and prior to SCT.
4. **Impact of allogeneic stem cell transplantation on MRD and Bcr-Abl kinase domain mutations in patients with Ph chromosome-positive ALL. HP Pfeifer, Frankfurt**

- **Aim**: To determine the impact of imatinib plus chemotherapy followed by allogeneic SCT on MRD and Bcr-Abl mutations in Ph+ ALL pts.
- Bcr-Abl mutations detected prior to SCT in a significant proportion (25%) of younger adult patients treated with imatinib and intensive chemotherapy. Allogeneic SCT appears to result in long-term elimination of mutant clones in the majority of patients. However, patients remain at risk of relapsing with previously undetectable TK mutations, some of whom are considered responsive to second generation ABL TK inhibitors.
5. Unrelated transplants for poor prognosis adult ALL: long-term comparative analysis based on the hematopoietic progenitor source. C. Ferra, Badalona

- Aim of the study: to compare the outcome of adult patients with unrelated transplant for poor prognosis ALL based on the hematopoietic source used for transplant.
- 137 adult patients (median 29 years [15-59], 82M/55F) with poor prognosis ALL received an unrelated transplant in 12 Spanish institutions from 2000 to 2007.
- UCB transplant, unrelated PBSCT and unrelated BMT are equivalent options for poor prognosis adult ALL patients without a sibling donor. However, all unrelated transplant modalities are associated with high transplant related mortality.
The presence of CD56/CD16 in T-ALL leads to worse survival and correlates with the expression of cytotoxic molecules. L. Dalmazzo, Ribeirão Preto

Characterization of Nup214-Abl1 positive T-ALL reveals genomic heterogeneity of the fusion gene presentation. C. Graux, Yvoir

Additional genetic features of Nup214-Abl1 positive pediatric T-ALL. M.P. Pisecker, Vienna

LCK is a critical signaling effector in Nup214-Abl1 positive T-ALL. K. De Keersmaecker, Leuven

Taf1-Nup214 is a new recurrent fusion in a subset (~3%) of adult T-ALL. P. Gorello, Perugia
Molecular characterization of chromosomal alterations in T-cell neoplasms by combining of FT-CGH and LM-PCR. G.K. Przybylski, Poznan

Rescue of genomic information in 72% of adult acute lymphoblastic leukemia (all) with normal/failed cytogenetics and identification of NF1 deletion as the hallmark of a subset of Notch1-mutated T-ALL. A GIMEMA study, C. Matteucci, Perugia

Identification by oligonucleotide arrays of a subset of T-ALL patients with myeloid-like gene pattern: potential mechanisms of transformation. S. Chiaretti, Rome
Identification of novel subgroups in T-ALL

Evidence of a subgroup of patients (n=5, 10%) characterized by the overexpression of myeloid genes: *myeloid-like cluster*. Last analysis 9/71 cases (12%).