

Session 10: CLL

119 DEL(13Q14.3) LENGTH MATTERS: AN INTEGRATED ANALYSIS OF GENOMIC, FISH AND CLINICAL DATA IN 169 CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) PATIENTS WITH 13Q DELETION ALONE OR NORMAL KARYOTYPE

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Introduction: CLL is the most common adult-onset leukemia in the Western world. The disease has a very heterogenous natural clinical course and survival after diagnosis can range from months to decades. The most frequent chromosomal aberration is del(13q14), targeting the DLEU2/MIR15A/MIR16B locus. When present as single FISH lesion, it is considered as a good prognosticator. Deletions at 13q14.3 are heterogeneous and an involvement of other transcripts mapped in the region has been proposed. Data have been recently presented suggesting a worse outcome for patients having larger del(13q14.3).

Aim: To evaluate this observation, we analyzed CLL patients, characterized by FISH as having a normal karyotype or del(13q14.3) alone, with a high density genome-wide DNA array.

Patients and Methods: DNA was extracted from consecutive diagnostic frozen samples, diagnosed and treated according to the NCI criteria, in 4 centers and analyzed with Affymetrix Human Mapping 6.0 arrays. Profiles were estimated using circular binary segmentation algorithm using 270 Caucasian HapMap profiles as reference dataset to normalize the CLL DNA profiles.

Results: 3 types of 13q losses were defined: type 1, loss of the DLEU2/MIR15A/MIR16B locus alone (58/169 cases, 34%), type 2 comprising also RB1 gene (24/169 cases, 14%) and type 3 extending for 10 Mb, thus beyond these two loci (n=13/169 cases, 8%). A disomic status 13q locus was present in 74/169 (44%) patients (13q wt). With a median follow-up of 60 months (range 0.2-314), the type of deletion significantly affected the outcome. Patients with larger deletions (type 2 and 3) presented a significantly worse time to treatment (TT) than type 1 patients (p=0.038 and 0.004, respectively). Type 1 and 3 behaved similarly to 13q wt cases, with only type 1 lesions associated with a better TT than 13q wt patients (p=0.022). While type 1 and type 2 lesions did not reach the median overall survival (OS), type 3 had a worse OS than 13q wt (p=0.018). Type 3 cases had significantly less commonly mutated IGHV genes.

Conclusions: Losses targeting a larger number of transcripts, including RB1 and DLEU7, are associated with a worse clinical outcome. These data prompt the need to better characterize the 13q14.3 deletion pattern at diagnosis to make a proper outcome estimate.

120 RITUXIMAB PLUS CHLORAMBUCIL (R-CHLORAMBUCIL) AS FIRST-LINE TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL): FINAL ANALYSIS OF AN OPEN-LABEL PHASE II STUDY

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Introduction: Rituximab plus fludarabine and cyclophosphamide is now widely used as first-line treatment for medically fit patients with CLL. For less fit patients chlorambucil is commonly used but achieves only modest response rates with few complete responses (CRs); thus more effective regimens are needed. We report the results of a multicentre Phase II study of R-chlorambucil as first-line treatment for CLL.

Methods: 100 patients with previously untreated CLL received six 28-day cycles of rituximab (500mg/m² Day 1 [375mg/m² in Cycle 1]) plus chlorambucil (10mg/m²/day Days 1-7). Response data were compared to case-matched data from 200 patients from the chlorambucil-only arm of an earlier UK study (LRF CLL4, 1994-2008) matched 1:2 by Binet stage, IgV_H mutation, 11q status by FISH, and age.

Results: Median age was 70 (43-86). The overall response rate (ORR) in all 100 patients was 80% (95% CI 70.8-87.3) with 12 patients (12%) achieving a CR, compared with 66% ORR and 6% CR in the case-matched controls (Table). Median PFS was 23.9 months. The regimen was well tolerated - most adverse events were grade 1 or 2.

Trial	N	CR (%)	ORR (%)	Stable/ progressive disease (%)	Not evaluable (%)	95% CI for ORR (%)
R-chlorambucil	100	12	80	17	3	[70.8, 87.3]
Chlorambucil	200	6	66	30	4	[59.0, 72.5]

Conclusions: R-chlorambucil is an effective and well-tolerated treatment for patients with previously untreated CLL, which appears to result in higher response rates than chlorambucil alone. R-chlorambucil is currently being evaluated in a randomised comparison with chlorambucil alone (CLL11).

121 FCR VS AUTOLOGOUS STEM CELL TRANSPLANTATION AS FIRST-LINE TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A COMPARISON OF TWO PROSPECTIVE STUDIES OF THE GCLLSG

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A recent prospective randomized trial has suggested that autologous stem cell transplantation (autoSCT) doubles progression-free survival (PFS) and treatment-free survival in comparison to conventional 1st-line chemotherapy without rituximab for CLL (Michallet et al, Blood 2010). In order to set this data into perspective with the current 1st-line gold standard, the fludarabine-cyclophosphamide-rituximab (FCR) regimen, we have compared retrospectively patients from the prospective GCLLSG CLL3 trial (autoSCT; 1996-2002) with the FCR arm of the GCLLSG CLL8 trial (2003-2006; Hallek et al, Lancet 2010). Eligible were all patients from CLL3 and CLL8 (FCR) who were <=60 years, were chemotherapy-naïve, and had complete central genomic work-up available. Patients with del 17p- were excluded. The primary objective of the study was to assess if autoSCT has superior PFS and time to CLL-specific retreatment (TTRT) over FCR.

Results: 110 of 169 patients from the CLL3 trial and 126 of 408 patients from the CLL8 (FCR) trial met the inclusion criteria. AutoSCT and FCR patients were well matched for age, time from diagnosis to study entry, serum thymidine kinase levels, FISH risk group, and IGHV status (unmutated 64% vs 68%). However, autoSCT patients had significantly higher beta2-microglobulin serum levels (3.3 vs 2.7 mg/dl) and were significantly more likely to be in Binet A stage at study entry (15% vs 3%). With a median observation time of surviving patients of 8.3 and 4.7 years, respectively, PFS of the autoSCT group was significantly longer than that of the FCR group (median 6.2 vs 4.3 years, p 0.009). This effect remained significant after multivariate adjustment for potential confounders (hazard ratio (HR) for FCR 1.66 (95%CI 1.11-2.5)). However, TTRT and OS were not different between autoSCT and FCR (4-year TTRT 75% vs 77%, HR for FCR 1.03, p 0.91; and 4-year OS 86% vs 90%, HR for FCR 1.32, p 0.39). Subgroup analyses did not reveal a significant TTRT benefit for autoSCT in any Binet, IGHV and FISH subset except for the pooled group of karyotypes other than 13q- single, 11q-, and +12 (p 0.023). The benefit of autoSCT in PFS but not TTRT might be explained with the more intense follow-up monitoring applied in the CLL8 trial, resulting in earlier detection of PFS events. Non-relapse mortality (NRM) was not significantly different between autoSCT and FCR (4-year NRM 7% vs 4%, p 0.68).

Conclusions: Although these results confirm that autoSCT is a highly effective 1st-line treatment for CLL, no significant clinical benefit of autoSCT over FCR could be observed.

122 THE BTK INHIBITOR PCI-32765 IS HIGHLY ACTIVE AND TOLERABLE IN PATIENTS WITH POOR-RISK CLL: INTERIM RESULTS FROM A PHASE IB/II STUDY.

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Introduction: Bruton's tyrosine kinase (Btk) is a downstream mediator of B-cell receptor (BCR) signaling. PCI-32765 (P) is a potent, irreversible inhibitor of Btk, causing inhibition of survival signaling, cellular chemotaxis and homing in CLL cells ex vivo. We report the interim results of an ongoing Phase Ib/II trial of P in treatment-naïve (TN) or relapsed/refractory (R/R) CLL.

Methods and Patients: This Phase Ib/II study is evaluating the safety and efficacy of P in 2 cohorts of CLL: 1) ≥ 65 years old with TN disease, and 2) R/R disease following at least 2 prior treatment regimens, one of which must have included fludarabine. P was administered PO QD for 28-day cycles until disease progression (PD). Doses of 420mg and 840mg QD were evaluated in separate cohorts of R/R patients; only the 420mg QD dose was evaluated in TN patients. Clinical response was evaluated according to standard criteria.

Results: 39 patients have been enrolled to the 420mg cohorts of the study (12 TN, 27 R/R). Median number of prior treatment regimens in R/R pts was 3 (2-10). 87% of pts had at least one poor-risk molecular feature: del17p 30%, del11q 21%, unmutated IgVH 70%. The majority of AEs have been mild in severity and not clearly related to P. Grade ≥ 3 AEs potentially related to P have occurred in 31% of pts. Grade ≥ 3 neutropenia and thrombocytopenia have occurred in $\leq 5\%$ of pts. No hepatic or renal AEs have been reported.

In evaluable pts with lymphadenopathy (LN), the rate of nodal response (LNR; $\geq 50\%$ reduction in target lesions) is 89% (25/28 pts). A transient increase in absolute lymphocyte counts (ALC) occurred in 75% of pts with measurable LN. LNR was similar in patients with or without poor-risk molecular features. Platelet counts have improved in 9/13 pts (69%) with baseline thrombocytopenia. At a median follow-up of 4 months, 34/39 pts remain on P. Reasons for discontinuation: pt decision n=2, AE n=2, PD n=1. Overall response by CLL IWG criteria and progression-free survival will be updated.

Conclusions: P is highly active with minimal toxicity in pts with either TN or R/R CLL, including molecular poor-risk pts.

123 SEQUENTIAL THERAPY OF FLUDARABINE, MITOXANTRONE AND CYCLOPHOSPHAMIDE (FMC) INDUCTION FOLLOWED BY ALEMTUZUMAB CONSOLIDATION IS EFFECTIVE AND SAFE IN PATIENTS WITH T-CELL PROLYMPHOCYTIC LEUKEMIA (T-PLL) - RESULTS FROM A MULTICENTER PHASE II TRIAL OF THE GERMAN CLL STUDY GROUP

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Background: T-cell prolymphocytic leukemia (T-PLL) is a very rare and generally refractory disease with a poor prognosis. The scarcity of available systematic trial data has largely prevented uniform therapeutic guidelines. To address improvement and prolongation of responses in T-PLL, we designed a prospective, multicenter phase-II study that adds a fludarabine-based poly-chemotherapy to the established most active single substance, namely alemtuzumab.

Patients and Methods: This multicenter phase-II trial evaluated response, survival, and toxicity of a novel regimen (FMC-A) in 25 patients with T-PLL (9 previously treated, 16 treatment-naïve). Induction by fludarabine, mitoxantrone, and cyclophosphamide (FMC, up to 4 cycles) was followed by alemtuzumab (A) consolidation (12 weeks, 30mg IV, 3x/week).

Results: The overall response rate (ORR) after FMC was 68%, comprising 6 complete remissions (CR) and 11 partial remissions (PR). Alemtuzumab consolidation, given to 21 patients, increased the ORR to 95% (10 CR; 10 PR). Median PFS for all 25 patients was 11.9 months (9.3-14.6 CI 95%), median PFS was 12.9 months for patients in CR as compared to 10.4 months for patients achieving a PR as their best response. Median OS was 17.1 months (12.1-22.1 CI 95%). There were no significant differences in ORR, OS, and PFS between the subsets of previously treated and treatment-naïve patients. PFS tended to be shorter for patients with high-level TCL1 oncoprotein expression ($p=0.05$). The most frequent grade 3/4 toxicity under FMC-A was myelosuppression. Only in the 21 patients treated with alemtuzumab a total of 12 CMV reactivations were observed, which were asymptomatic in 3/12, while 9/12 experienced a clinically relevant CMV infection.

Conclusion: Sequential FMC-A induces response rates associated with survival that are among the best reported in T-PLL. It is thus a very effective and also safe regimen, but nearly all patients, regardless of quality of response eventually relapse. Therefore, a key issue remains the search for the most optimal front-line regimen consisting of an alemtuzumab backbone to bridge towards a potentially curative allogeneic stem cell transplantation.

124 CLADRIBINE GIVEN SUBCUTANEOUSLY FOR FIVE DAYS HAS EQUIVALENT EFFICACY TO AND LOWER TOXICITY THAN CLADRIBINE GIVEN FOR SEVEN CONSECUTIVE DAYS IN PATIENTS WITH HAIRY CELL LEUKEMIA

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Introduction: Cladribine (2CdA) given 0.1 mg/kg/day for 7 consecutive days intravenously or subcutaneously is very effective in HCL, although it may cause infections in a high proportion of patients.

Material and methods: In the Italian multicentre ICGHCL2004 clinical trial, toxicity and efficacy of sc2CdA given 0.1mg/kg/die for 5 (arm A) or for 7 consecutive days (arm B) was prospectively evaluated in centrally verified classic HCL requiring first treatment. Study endpoints were *i*) early grade 3-4 toxicity, *ii*) response to treatment, *iii*) treatment free interval (TFI), *iv*) relapse free survival (RFS), *v*) time to second tumor (TTST) and *vi*) overall survival (OS). TFI and RFS were measured as the time elapsed from sc2CdA initiation to second treatment because of new progression or failure to sc2CdA in all patients and in responsive patients only, respectively.

Results: 148 classical HCL entered the study. Clinical and laboratory parameters prior to treatment were equally balanced in the two arms. Overall hematological toxicity was no different among the two treatment arms. However, a higher non hematological toxicity was observed in arm B ($p=0.19$). Non hematological toxicity was mainly represented by infections/FUO that were more frequent in arm B (17/71, 23.9%) than in arm A (8/77, 10.4%, $p=0.28$) and that resulted in a hospitalization rate higher in arm B (20/71, 28.2%) than in arm A (9/77, 11.7%, $p=0.12$). Onehundred-forty patients (94.6%) had a beneficial response. Responses were equivalent in the two arms, with 72/77 (93.5%) beneficial responses in arm A versus 68/71 (95.8%) beneficial responses in arm B. After a median follow-up of 42 months (range 16-72), 5 year TFI, RFS, TTST and OS were 68%, 72% 88% and 95%, respectively. No differences of TFI, RFS, TTST and OS were observed in the 2 arms.

Conclusions: This study indicates that sc2CdA given at 25% reduced doses (0.5 mg/kg) has equivalent activity and significantly lower toxicity than sc2CdA at standard doses (0.7 mg/kg). The reduced infection rates and hospitalization rates of sc2CdA have important clinical and pharmaco-economic implications.