Impact of MRD Eradication on Survival Outcomes in CLL Patients with Different IGHV Mutation Status

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Context: MRD eradication and IGHV-status could be considered progesterone factors for overall (OS) and progression-free survival (PFS) in CLL patients. Objective: To analyze the impact of MRD and IGHV-status on survival outcomes in CLL patients after first-line standard BR immunochemotherapy. Design: Prospective study included 186 treatment-naive patients with a confirmed diagnosis of CLL (median age 61 years). All patients were treated with a BR-regimen from 2012 to 2015. Patients: All patients received standard BR (rituximab 375 mg/m² − 500 mg/m² D1 or D0, bendamustine 90 mg/m² D1-D2 x 6 cycles) in an inpatient setting. CLL MRD was measured in bone marrow by standardized 4-color flow cytometry (Rawstron et al. 2007). For this report 115 patients with known BM MRD levels after 3nd and 6 cycles were analyzed. Additionally, 12 patients with SD/PD were included in the MRD(pos) group (total N=127). IGHV mutation status was evaluated in accordance with ERIC recommendations. Patients were divided in two groups depending on IGHV-status (n=164): IGHV(mut) – 55 patients (33.5%) and IGHV(unmut) - 109 patients (66.5%). Results: MRD eradication was achieved in 40 (31.5%) out of 127 patients. MRD negativity (MRD-neg) (p<0.001) and IGHV(mut)-status (p=0.002) had a significant impact on PFS. Median OS was not reached in all subgroups of patients, however a trend for lower OS was seen in IGHV(mut) patients with a persistence of MRD after 6 cycles. At a median follow-up of 39 mos MRD-neg patients with IGHV(mut)-status had no PD or deaths. Achievement of the MRD-negativity after the 3rd cycle significantly improved PFS (p=0.03). Also, MRD-neg patients had longer PFS regardless of the clinical response (CR or PR). There was no significant difference in PFS between MRD-pos patients with IGHV(mut) and IGHV(unmut) CLL (p=0.188). All these patients had poor survival in comparison to the MRD-neg group. The worst survival rates were observed in IGHV(unmut) patients with MRD persistence (p=0.009). Conclusions: Patients who achieve MRD-neg remission after 1st line BR have prolonged PFS. This is mostly evident in patients with IGHV(mut) CLL. Thus, both IGHV mutation status and MRD could be considered prognostic factors for CLL patients. Tailored treatment approaches might be needed for patients who don’t achieve MRD(neg) remission after 1st line BR. Keywords: CLL, BR, IGHV-status, MRD, chronic lymphocytic leukemia

Effect of Dose Modifications on Response to Duvelisib in Patients with Relapsed/Refractory (R/R) CLL/SLL in the DUO Trial

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Context: Duvelisib, a first-in-class oral dual PI3K-δ,γ inhibitor, is approved for treatment of R/R CLL/SLL after ≥2 prior therapies. In the phase 3 DUO trial, duvelisib 25 mg BID significantly improved efficacy vs ofatumumab in patients with R/R CLL/SLL. Treatment-emergent AEs (TEAEs) of special interest (AESIs) were moderate and manageable with early intervention and dose modification. Objective: To examine dose modification patterns and their impact on response to duvelisib in the DUO trial. Design: Dose interruptions (DIs) or reductions (DRs) were permitted per study protocol to manage TEAEs. Responses were assessed by IRC. Results: Among 158 duvelisib-treated patients, median duration of exposure was 11.6 months. DIs occurred more frequently than DRs (80% vs 27%). The most common AESIs leading to DI were diarrhea/colitis (28%), infections (27%), cutaneous reactions (13%), and neutropenia (12%). Among 118 responders, median time to first response was 1.9 months and median duration of response was 11.1 months. Median time to first DI was 3.9 months and median duration was 15 days. Response to duvelisib was improved or maintained in most patients evaluated for response who had ≥1 DI for ≥1 week (84%) or >2 weeks (82%) followed...
Abstracts

by ≥3 weeks on duvelisib. In a landmark analysis, median PFS was similar in patients with and without DI for >1 week (17.8 vs 16.3 months) or >2 weeks (17.8 vs 16.3 months) within the first 3 months. The median time to DR after CR/PR was 5.6 months (n=25) and median duration was 3.4 months. Median time to onset across AESIs ranged from 2.2 to 4.3 months and median duration across AESIs was up to 4 weeks. Proportions of patients experiencing AESIs were stable or decreased over time after 3-6 months: 0-3 months, 64%; >3-6 months, 63%; >6-9 months, 47%; >9-12 months, 52%, and seldom led to discontinuation of duvelisib (≤10%). Conclusions: DIs/DRs can contribute to the effective management of TEAs with duvelisib. These findings suggest that DIs of >1 week do not negatively impact response to duvelisib or PFS. Keywords: dose modification, duvelisib, chronic lymphocytic leukemia, PI3K, CLL.

CLL-046
Five-Year Follow-Up After Ibrutinib Therapy for First-Line Treatment of Chronic Lymphocytic Leukemia
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Context: Ibrutinib, a first-in-class, once-daily BTK inhibitor, is approved in the US for treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The RESONATE-2 study evaluated first-line ibrutinib vs chlorambucil in older patients with CLL/SLL. Objective: Report efficacy and safety with a 5-year median follow-up of first-line ibrutinib in CLL/SLL. Design: Phase 3, international, open-label, randomized study (2013-ongoing) (PCYC-1115/1116; NCT01722487, NCT01724346). Patients: Patients aged ≥65 with previously untreated CLL/SLL without 17p deletion (N=269). Interventions: Patients randomized 1:1 to ibrutinib 420 mg/day continuously or chlorambucil 0.5–0.8 mg/kg for ≤12 cycles. Patients were eligible to receive ibrutinib after disease progression on chlorambucil. Main Outcome Measures: PFS, ORR by investigator per iwCLL 2008 criteria, and safety. Results: Baseline characteristics were balanced. With a median of 5 years of follow-up (range, 0.1–66 months), PFS benefit continued for ibrutinib vs chlorambucil, with hazard ratio (HR) 0.15 (95% confidence interval [CI]: 0.10–0.22). 6-month PFS estimates for ibrutinib were 70% versus 12% for chlorambucil. Sixty-month OS favored ibrutinib (83%) versus chlorambucil (68%), despite 57% of chlorambucil patients crossing over to ibrutinib. The subgroup of patients with one or more high prognostic risk features of unmutated IGHV, 11q deletion, and/or TP53 mutation had superior outcomes with ibrutinib versus chlorambucil (PFS: HR 0.08 [95% CI: 0.05–0.15]; OS: HR 0.37 [95% CI: 0.18–0.74]). With ibrutinib, ORR including partial response with lymphocytosis was 92%; complete responses increased to 30% (from 11% at the 18-month median follow up). Most common grade ≥3 AEs included neutropenia (13%), pneumonia (12%), and hypertension (8%). Rates of most AEs (any grade) and dose reductions due to grade ≥3 AEs decreased over time. The majority of patients (58%) starting ibrutinib remain on ibrutinib. Patients responded to subsequent therapies, including chemoimmunotherapy and alternate kinase inhibitors, following ibrutinib. Conclusions: Single-agent ibrutinib demonstrated sustained PFS and OS benefit with >5 years of follow up, including for patients with high-risk genomic features. Nearly three-fold more patients achieved CR/CRi, >50% of patients remain on continuous ibrutinib, and no new safety signals have emerged. Funding: Pharmacyclics LLC, an AbbVie Company. Keywords: ibrutinib, long-term follow up, chlorambucil, targeted therapy, CLL, chronic lymphocytic leukemia.

CLL-069
CLL-Derived Exosomes Reprogram Resident Cells to Become CLL Supportive Cells
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Context: CLL-derived exosomes shape their own fate. Specifically, we ask whether exosomes derived from CLL cells are taken-up by other cells and render them to become "tumor-supportive cells". Since endothelial cells are in close proximity to CLL cells in the peripheral blood, bone marrow