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What's new in the management of chronic lymphocytic leukemia? 2008 ASH Review (New York Medical College, January 31, 2009)

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The 2008 ASH Annual Meeting featured several important abstracts highlighting advances in the treatment of chronic lymphocytic leukemia (CLL).

Abstract 43 [1] retrospectively compared results of a phase II study of pentostatin and rituximab (PR) to previously published results using pentostatin, cyclophosphamide and rituximab (PCR) [2]. The pentostatin dose was increased to 4 mg/m^2 in the PR regimen, but demographics of patients in both studies were similar [1]. Overall response rate (OR) and complete response (CR) rates were similar for PR (79%, 30%) and PCR (91%, 41%), but median progression free survival (PFS) was significantly shorter for PR (12 months vs. 31 months) [1]. These results supported previous findings that the addition of cyclophosphamide to fludarabine improves OR, CR and PFS [3-5].

Abstract 325 presented results of the German CLL Study Group (GCLLSG) CLL8 study randomizing 817 previously untreated patients to fludarabine and cyclophosphamide (FC) or fludarabine, cyclophosphamide and rituximab (FCR) [6]. OR, CR and median PFS favored FCR (93%, 45%, 43 months) over FC (85%, 23%, 32 months), although 2-year overall survival (OS) was similar (91% vs. 88%). Abstract 326 demonstrated that median PFS depended upon the ability to eradicate minimal residual disease (MRD) in the peripheral blood, with PFS increasing from 15 months (MRD $\geq 10^{-2}$) to 34 months ($10^{-4} \geq$ MRD $>10^{-2}$) to not reached (MRD $<10^{-4}$) with increasing eradication of MRD [7]. Furthermore, 67% of patients receiving FCR achieved MRD $<10^{-4}$, compared to only 34% of FC patients, thus accounting for the improved PFS with FCR.

Abstract 327 randomized 184 patients (80% previously untreated, 20% relapsed) to PCR or FCR, using the MSKCC PCR regimen (pentostatin dose 4 mg/m^2) and the Johns Hopkins FCR regimen (fludarabine 20 mg/m^2 days 1–5, cyclophosphamide 600 mg/m^2 day 1). The primary endpoint, incidence of grade 3–4 infections, was similar for PCR (34%) and FCR (31%). Only 50% of patients in both arms completed therapy, resulting in surprisingly low OR and CR rates for PCR (45%, 7%) and FCR (58%, 17%). The trial was stopped early, so there were no statistically significant differences between the two arms, and no PFS data was presented. Nonetheless, abstract 327 indicated that results from academic centers may not necessarily be reproducible in the community [8].

Abstract 2095 updated results of a phase II study of cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR) in 48 previously untreated patients with high-risk features [9]. OR and CR were 94% and 69%, respectively, with OR 77% and CR 54% in 13 patients with del (17p13). Grade 3–4 neutropenia and thrombocytopenia were observed in 71% and 42% of patients, respectively, and 6% and 27% of patients developed major and minor infections, respectively.

Abstract 2091 updated results of a phase III study randomizing 319 previously untreated patients to chlorambucil or bendamustine [10]. OR, CR and median PFS favored bendamustine (67%, 32%, 21.5 months) over chlorambucil (30%, 2%, 8.3 months), although bendamustine caused greater hematologic toxicity (40% vs. 19%), especially grade 3–4 neutropenia (23% vs. 9%).

Two studies of lenalidomide in previously untreated patients were presented [11,12]. Abstract 44 summarized results of a phase I study in 25 Canadian patients [11]. Due to grade 5 sepsis and grade 3–4 tumor lysis, the dose was decreased from 25 mg to 2.5 mg and then escalated to 10 mg daily for 21 days every 28 days. Toxicity included fatigue (78%), tumor flare (78%), rash (48%) and grade 3–4 neutropenia (43%). OR and CR were 65% and 0%, respectively. Abstract 45 presented a study in 43 elderly patients age 65 or older [12]. Lenalidomide was given continuously, and 5–10 mg daily was the median delivered dose. Grade 3–4 myelosuppression and tumor flare were observed in 26% and 44% of patients, respectively. OR and CR were 54% and 0%, respectively. While lenalidomide is clearly active in CLL, the absence of CR in previously untreated patients was disappointing.

Abstract 47 presented a phase II study giving high dose methylprednisolone 1000 mg/m^2 day 1–3 every four weeks and weekly rituximab (total dose 4500–6750 mg/m^2) to 28 patients [13]. OR and CR were 96% and 32%, respectively. Patients were lesser splenomegaly and lower beta-2-microglobulin levels were more likely to respond.

In the relapsed setting, abstract 329 presented final results of the GCLLSG CLL2H study which administered subcutaneous alemtuzumab to 103 relapsed patients, many of whom had high-risk features [14]. Infusion toxicity was minimal, but grade 3–4 anemia (56%), thrombocytopenia (57%), anemia (49%), cytomegalovirus reactivation (8%) and non-CMV infection (29%) were significant toxicities. Seventy-five patients died; 56% died of progressive CLL, and 31% died of infection. OR (34%), CR (4%) and median PFS (7.7 months) were similar to the results achieved by intravenous alemtuzumab in the pivotal CAM211 study [15].

Abstract 330 summarized a phase II GCLLSG trial administering bendamustine 70 mg/m2 on day 1–2 and rituximab 500 mg/m2 on day 1 to 81 relapsed CLL patients [16]. OR and CR were 77% and 15%, respectively. Twelve of 13 patients (92%) with del (11q22), 4/9 patients (44%) with del (17p13), and 29/39 patients (74%) responded, indicating that bendamustine is active in high-risk relapsed CLL.

Abstract 46 presented combined phase I/II results of flavopiridol (alvocidib) in 116 relapsed patients, 70% of whom were fludarabine-refractory [17]. OR in this high-risk population was 47%. Furthermore, 19/39 del (17p13) patients (49%), 28/47 del (11q22) patients (60%) and 22/52 complex karyotype patients (42%) responded, demonstrating the activity of flavopiridol in poor-risk groups with limited therapeutic options. Forty-one of 85 patients (48%) with bulky lymphadenopathy > 5 cm responded. Median PFS in responders was 10–12 months across all risk groups. A registration study is ongoing.

Finally, abstract 328 presented a pivotal phase II study of the fully humanized anti-CD20 antibody ofatumumab (HuMax-CD20) in relapsed patients refractory to both fludarabine and alemtuzumab (DR, n = 59) or with bulky lymphadenopathy refractory to fludarabine (BFR, n = 79) [18]. OR, time to next therapy, and OS were similar for the DR (51%, 9.0 months, 13.7 months) and BFR groups (44%, 7.9 months, 15.4 months). These results have been submitted for FDA approval.

Competing interests

The authors declare that they have no competing interests.

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