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Oral Session

Chronic Lymphocytic Leukemia - Therapy, Excluding Transplantation

Phase III Trial of Fludarabine, Cyclophosphamide, and Rituximab Vs. Pentostatin, Cyclophosphamide, and Rituximab in B-Cell Chronic Lymphocytic Leukemia

Craig Reynolds, MD[1], Nicholas Di Bella, MD[2], Roger M. Lyons, MD[3], William J Hyman, MD[4,*], Gary L. Lee, MD[5,*], Donald A Richards, MD, PhD[4,*], Gerald J. Robbins, MD[6,*], Mark Vellek, MD[7], Kristi A Boehm, MS[8,*], Feng Zhan, PhD[8,*] and Lina Asmar, PhD[8,*]

[1] US Oncology Research, Inc., Houston, TX and Ocala Oncology Center, Ocala, FL, USA, [2] US Oncology Research, Inc., Houston, TX and Rocky Mountain Cancer Centers, Aurora, CO, USA, [3] US Oncology Research, Inc., Houston, TX and Cancer Care Centers of South Texas, San Antonio, TX, USA, [4] US Oncology Research, Inc., Houston, TX and Tyler Cancer Center, Tyler, TX, USA, [5] US Oncology Research, Inc., Houston, TX and Willamette Valley Cancer Center, Eugene, OR, USA, [6] US Oncology Research, Inc., Houston, TX and Florida Cancer Institute, New Port Richey, FL, USA, [7] US Oncology Research, Inc., Houston, TX and Missouri Cancer Associates, Columbia, MO, USA, [8] US Oncology Research, Inc., Houston, TX, USA

Abstract

Purine analog-based regimens have emerged as highly active regimens in the treatment of chronic lymphocytic lymphoma (CLL). Promising results have been reported with the combination of fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) by Keating and colleagues at the University of Texas M.D. Anderson. A previous USOR trial, as well as a Mayo clinic trial, evaluated the combination of pentostatin (P), cyclophosphamide (C), and rituximab (R) (PCR); results suggested similar efficacy with less infectious complications than that seen with FCR. The current multicenter, randomized, community-based trial was conducted to compare FCR and PCR in previously untreated or minimally treated B cell CLL.

The primary endpoint was infectious complications with efficacy and safety as secondary endpoints. Correlative studies of immune function were conducted by Kay and colleagues at the Mayo Clinic and will be reported separately. Patients (pts) were assigned to either PCR (P 4 mg/m^2 Day 1, C 600 mg/m^2 Day 1, R 375 mg/m^2 Day 1) (2 1-day cycles) or FCR (F 20 mg/m^2 Day 1–5, C 600 mg/m^2 Day 1, R 375 mg/m^2 Day 1) (28-day cycles). In both regimens the first dose of R 100 mg/m^2 was given on Day 8 Cycle 1 and the remainder of the 375 mg/m^2 dose was given on Day 9; in subsequent cycles the entire 375 mg/m^2 dose was given on Day 1. 92 pts were randomized to each group (N=184). Groups were well balanced for sex, race, and age. Stage II/III/IV were 41%/22%30% for FCR vs 55%/17%/22% for PCR and ECOG PS 0/1/2 were 74%/22%/1% for FCR vs 62%/34%/2% for PCR; ~20% of pts in both groups had received prior chemotherapy; 80% were previously untreated. The infection rate (temperature ☐101 requiring antibiotics) in FCR was 30.7% vs 33.7% in PCR (p=0.67) while infective events (temperature ☐101°F w/o symptoms or <101°F with symptoms was 36.8% in FCR vs 43.5% in PCR (p NS); 29 (33%) FCR patients were hospitalized compared to 35 (41%) of PCR patients; total number of hospitalization days was 258 with FCR and 377 with PCR (p NS). Complete remissions were achieved in 15 (17%) FCR pts and 6 (7%) PCR pts, while the overall response rate (ORR) including CR+PR+nPR was 57.5% in FCR vs 45% in PCR; SD was best response in 29% of FCR and 48% of PCR pts. The difference in CR was significant (P=0.04) between groups; however, ORR was not (P=0.13). Updated results will be presented at the meeting. The most frequent Grade 3–4 treatment related AEs (for FCR/PCR) were: neutropenia (64%/57%), leukopenia (33%/17%), thrombocytopenia (10%/4%) Grade 3–4 infections with FCR vs PCR were: febrile neutropenia (4.5%/arm), fever (2.3% vs 4.5%), infection (0% vs 3.4%), urinary tract infection (1.1% vs 0%), pneumonia (4.5% vs 0%), and sepsis (1.1%/arm). As of May 2008, 10 FCR and 17 PCR pts have died; 2 FCR deaths (pneumonia and sepsis) were infection-related. ~50% in each group completed the protocol; 28% of FCR and 27% of PCR pts discontinued due to AEs). We conclude that both PCR and FCR have significant activity in CLL and can be given safely in the community setting. Both regimens possess significant toxicity and response rates in this multi-institution, community-based randomized trial were lower than previous phase II trials of previously untreated patients. This trial did not demonstrate a lower infection rate with PCR using pentostatin at the 4 mg/m^2 dose level. In early follow-up, no statistically significant differences with respect to overall response rate or survival were observed between FCR and PCR, although the CR rate was significantly higher with FCR. This research was supported, in part, from a research grant from Hospira, Inc.

Footnotes

Corresponding author

Disclosures: Lyons: *Amgen:* Consultancy; *GlaxoSmithKline:* Consultancy; *Novartis:* Consultancy. **Off Label Use:** Pentostatin inhibits adenosine deaminase (ADA) and promotes apoptosis. The substitution of pentostatin for fludarabine in combination with the cyclophosphamide+rituximab may result in similar response rates and duration of response and with more tolerable toxicities in patients with previously untreated or previously treated CLL..

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