Alemtuzumab and Rituximab for Therapy of Patients with Early Stage High Risk CLL: Report of a planned interim analysis

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Introduction

- Standard for CLL = treat obvious clinical progression
  - Earlier intervention not of proven benefit
  - Therapy is non curative
- Biological prognostic markers – could patients with early identification of high risk disease benefit from treatment?
- Is combined lymphocyte targeted monoclonal antibody therapy safe and effective?
Hypothesis

In early clinical stage CLL, combination MoAb therapy with alemtuzumab and rituximab will eliminate or greatly decrease the size of the high risk clone characterized by 17p13-, 11q22-, or UM IgVH together with either ZAP70+ or CD38+. 
Methods

Patients

• Enrollment
  • Target = 30 patients
  • Planned interim analysis after 11
• Previously untreated CLL
  • Rai stage 0 –II
  • No NCI-WG 1996 treatment criteria
• High risk disease
  • 17q13- or
  • 11q22- or
  • UM IgVH + (CD38+ and/or ZAP-70+).
Methods

Therapy

• Alemtuzumab
  • Subcutaneous
  • Dose escalation: 3 mg - 10 mg - 30 mg/d (d 1-3) then
  • 30 mg Monday, Wednesday and Friday x 4 weeks

• Rituximab (375 mg/m²/week IV)
  • x 4 weeks
  • Start day 8 of alemtuzumab Rx

• Prophylaxis x 7 months
  • Herpes virus
  • PCP

• CMV monitoring by PCR
Methods
Response Evaluation

• NCI-WG 1996 criteria
• Bone marrow studies with IHC
• MRD
  • Peripheral blood
  • Flow cytometry (CD19+/CD5+/CD79bdim)
Patients

n = 11

- Median age 62 years (29 – 75)
- 6 males: 5 females
- High risk factors
  - 17p13- 4
  - 11q22- 3
  - UM IgVH + CD38+/ZAP-70+ 4
- Median Dx to Rx 11 months (2-72)
Patients

• Clinical stage (Rai)
  • 0  3
  • I  5
  • II  3

• CBC at diagnosis
  • LY#  25.6 x 10^9/L (15.9 – 81.8)
  • Hgb  14.4 g/dL (12 – 15.8)
  • platelet  171 x 10^9/L (125 – 312)
Results - Safety

• Serious adverse events
  • CMV reactivation (n = 1)
  • Febrile drug reaction (SMT/TMP) (n = 1)
• Grade 3-4 adverse reactions (no interventions)
  • Leukopenia n = 4
  • Neutropenia n = 2
  • Anemia n = 1
  • Elevated ALT n = 1
  • Skin reactions n = 1
• Skin reactions to alemtuzumab
  • All patients dose 1
  • Minimally symptomatic
  • All resolved with ongoing treatment
• No “first dose” reactions
Results - Response

- Overall response rate = 100%
  - CR 5
  - nPR 3
  - PR 3

- Duration of response
  - Progression free survival figure 1

- One death
  - off study
  - complications of alloPBSCT
Figure 1: Progression Free Survival

% Alive and Progression Free vs Time (months)
Figure 1

Kaplan-Meier analysis of progression free survival in the 11 patient cohort
Minimal Residual Disease

- CR + BM IHC negative + MRD negative
  - n = 4
  - Duration MRD - 120 – 210 days (figure 2)
  - All in sustained clinical CR at 12 months
  - Duration of response 12+ – 21+ months
Figure 2: Serial Measurements of MRD in Patients Achieving MRD negative CR (n = 4)
Minimal residual disease (MRD) was measured in peripheral blood with 3 color flow cytometry using antibodies against CD5, CD19 and CD79b (sensitive to $1:10^4$ cells). Four patients achieved clinical CR with normal BM examination, no residual disease on immunohistochemical analysis and had negative MRD. All these patients achieved negative/minimal MRD by 1 week after initiation of therapy and duration of MRD negative assays was 120 -210 days. All were in sustained clinical CR at 12 months.
Conclusion

- Alemtuzumab and rituximab is effective & tolerable therapy for early stage high risk CLL
- All patients responded to therapy
- No long term sustained MRD negative remissions
- Efficacy of therapy needs to be improved:
  - Addition of drugs that enhance MoAb activity
  - Maintenance therapy
Disclosure

• Genentech Grant  (P.I. C. Zent)
• Berlex Grant  (P.I. C. Zent)
• Iowa/Mayo Lymphoma SPORE  
  (NIH Grant – P.I. G. Weiner)
• Off-label use of drugs:
  – Alemtuzumab
  – Rituximab
ALEMTUZUMAB AND RITUXIMAB FOR THERAPY OF PATENTS WITH EARLY STAGE HIGH RISK CLL: REPORT OF A PLANNED INTERIM ANALYSIS

The current standard of care for CLL is to treat only patients with obvious clinical progression because earlier intervention is not of proven benefit. However, the discovery of more accurate prognostic markers for CLL could change that paradigm. The predictors of more aggressive disease include 17p13 deletion (17p13-), 11q22-3 deletion (11q22-), unmutated (UM) immunoglobulin heavy-chain variable region (IgVH), and expression of ZAP-70 and CD38, all of which can be detected in early CLL. In addition, newer monoclonal antibody (MoAb) therapies provide effective treatment options with less toxicity than conventional chemotherapy. The combination of alemtuzumab and rituximab is of interest because of non-overlapping mechanisms of action. In addition, alemtuzumab is effective therapy for patients with defects in the p53 apoptotic pathway that are more resistance to purine analogue therapy. MoAb therapy is likely to be most efficacious in earlier stage CLL. In this study we tested the hypothesis that combination monoclonal antibody therapy with alemtuzumab and rituximab could be safe and effective therapy for patients with early stage high risk CLL.

The clinical trial was approved by the Institutional Review Board and has enrolled 20 of 30 planned patients at Mayo Clinic Rochester since January 2005. All patients with previously untreated CLL (Rai stage 0 –II) not meeting NCI-WG 1996 treatment criteria were evaluated for high risk disease (1. 17q13-, 2. 11q22-, or 3. UM IgVH and CD38+ and/or ZAP-70+). Treatment duration was 30 days (subcutaneous alemtuzumab dose escalation, 3 mg - 10 mg - 30 mg on days 1-3) followed by 30 mg Monday, Wednesday and Friday for 4 weeks starting on day 6. Rituximab (375 mg/m²/dose IV) was administered weekly for 4 weeks staring on day 8. All patients received prophylactic therapy to prevent pneumocystis pneumonia and herpes virus reactivation. Cytomegalovirus reactivation was monitored with molecular methods for
viral DNA. Response was evaluated using NCI-WG (1996) criteria and minimal residual disease (MRD) was measured in peripheral blood using highly sensitive flow cytometry (1:10⁴) for CD19+/CD5+/CD79b- lymphocytes.

The planned interim analysis reports completed treatment on the first 11 patients. The median age of patients was 62 years (29 – 75) with 6 males and 5 females. The qualifying high risk features were 17p13- (n = 4), 11q22- (n = 3), and UM IgVH + CD38+ +/- ZAP-70+ (n = 4). Median time from diagnosis to treatment was 11 months (2-72). Two patients had serious adverse reactions requiring intervention (CMV reactivation with multiorgan disease responsive to treatment and febrile drug reaction caused by sulfamethoxazole/trimethoprim). Other more severe adverse reactions not requiring interventions were leukopenia (n = 4), neutropenia (n = 2), anemia (n = 1), and elevated ALT (n = 1). All patients had initial skin reactions to subcutaneous alemtuzumab (one grade 3), but these were minimally symptomatic and all resolved with ongoing treatment. There were no “first dose” reactions. All patients responded to therapy with 5 complete responses (4 of these no detectable disease on highly sensitive testing i.e. MRD negative), 3 nodular partial responses, and 3 partial responses. Median duration of response has not yet been reached at median follow up of 11.7 months (6.5 – 14.9). Patients with a MRD negative CR had recurrence of detectable MRD at 120 – 210 days after completing therapy but all remain in clinical CR. One patient died off study of complications of a myeloablative allogeneic transplant for progressive CLL.

These results show that alemtuzumab and rituximab is effective and tolerable therapy for early stage high risk CLL. All patients responded with 36% of patients achieving a MRD negative CR. However, serial MRD assays showed that the CLL clone was not deleted. Although promising, this treatment approach requires further improvement.