Lymphoproliferative Disorders

The efficacy of alemtuzumab for refractory chronic lymphocytic leukemia in relation to cytogenetic abnormalities of p53

We reviewed the efficacy of alemtuzumab in the treatment of 28 patients with refractory chronic lymphocytic leukemia (CLL) in whom p53 status was known. Overall responses of 53.6% (complete responses 17.9%) were attained with no significant difference between patients with (50%) or without (55%) p53 deletion (p=0.214). We confirm the efficacy of alemtuzumab in refractory CLL irrespective of p53 deletions, and advocate its introduction earlier in disease course.

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p53 abnormalities predict poor response to fludarabine in chronic lymphocytic leukemia (CLL) whether the drug is used as second[1] or first line treatment.[2] Options for patients with p53 abnormalities include alemtuzumab[3,4] and high dose methlylprednisolone.[5] Both a recent case series,[4] and interim analysis of the CLL2H trial[6] confirm the efficacy of alemtuzumab in patients with p53 abnormalities. No other series specifically address this issue. We reviewed the use of alemtuzumab in CLL patients, focusing on those with p53 deletions.

A database of CLL patients receiving alemtuzumab was reviewed and patients for whom p53 deletional status could be assessed (n=28) by fluorescent *in situ* hybridization (FISH) were selected. Alemtuzumab was given at conventional doses (5 mg, 10 mg, 30 mg) followed by 30 mg three times a week to maximum response or toxicity, by intravenous (n=24) or subcutaneous (n=4) routes, and used with steroids (n=3) or rituximab (n=1) in cases with bulky nodes. Complete remission (CR), partial remission (PR), progressive disease (PD), or stable disease (SD) were defined using modified NCI criteria. Nodular PR (nPR) was also identified.

p53 deletions were present in eight (28.6%) patients (Table 1), and detected in >20% of cells in six of these eight cases. The median total alemtuzumab dose was 795 mg (range 160-1860), over 8 weeks (range 3-18). Dosage showed no correlation with response. The overall response rate (ORR) was 53.6% (CR 18%, PR 36%, SD 36%, 10% PD) with no significant difference (p=0.214) between patients with (ORR 50%; all PR) and without (ORR 55% - CR 25%; PR 30%) p53 deletions. Although no complete remissions were recorded among patients with p53 deletion, two patients were completely cleared of bone marrow disease and had normalized white cell counts, falling short of complete remission solely because of persistent cytopenias. Another patient (p53 deleted) fell short of nodular partial remission because of cytopenia, while another refused bone marrow biopsy, thus maximum assessable response was partial remission. Response quality was equivalent or superior to best previous response in 57% of cases. Four of the six patients with >20% of p53-deleted cells achieved partial remission and two had stable disease.

Patients lacking p53 deletions, but showing 11q23 deletions (n=5) had a 20% response (PR) whereas among those with neither (n=13), 61.5% achieved a response (CR 38.5%; PR 23%). Significant leukocyte reductions occurred in all cases (p<0.001). Alemtuzumab re-treatment was possible in six patients, one of whom received four separate courses (p53 non-deleted). Richter's transformation (n=2) was refractory to alemtuzumab treatment. Two patients, both p53 non-deleted, improved responses with alemtuzumab prior to stem cell transplantation. Toxicity was observed in 14 patients with asymptomatic cytomegalovirus (CMV) reactivation (n=5), cytopenias with infection (n=3), recurrent infections (n=1), persistent neutropenia (n=2), herpes zoster (n=1), and anorexia (n=1). One patient suffered fatal pulmonary CMV. Two further deaths were due to progressive disease. Time to progression, evaluable in 10 patients, ranged from 2.5-22.2 months (median 4 months) from the end of therapy.

Table 1. Summary of patients' clinical and laboratory characteristics.

Feature	*Result*
Median age at diagnosis /years (range)	50 (28-74)
Gender, male/female	25/3
Binet stage at treatment	
A progressive	5 (17.9%)
B	6 (21.4%)
C	17 (60.7%)
Median time from diagnosis, months (range)	68.4 (2.4-329.9)
Median number of previous therapies (range)	4 (1-11)
Prior fludarabine therapy	26 (92.9%)
Prior autologous stem cell transplantation	2 (7.1%)
Refractory/intolerant* to last course of fludarabine	16/24 (66.7%)
Hierarchical ranking of cytogenetic abnormalities	
Patients with del(17)(p13.1)	8/28 (28.6%)
Patient with del(11)(q23)	5/25 (20%)
Patients with trisomy 12	2/25 (8%)
Patients with del(13)(q14)	7/24 (29.2%)
Patients with normal interphase cytogenetic profile	1/24 (4.2%)

**one patient developed severe autoimmune hemolytic anemia.*

Table 2. Summary of data from reports of alemtuzumab treatment in patients with CLL possessing deletions of p53.

Authors	*Number*	*Number with p53 deletions*	*Overall response in p53 deleted group*
Lozanski *et al.*[4]	36	15	40%*
Stilgenbauer *et al.*[6]	50	13	53.8%
Osuji *et al.* (present paper)	28	8	50%*

**no complete remissions documented.*

CLL patients possessing p53 deletions and/or mutations show inferior prognosis.[7] A dose-dependent effect of p53 deletion on responses of untreated patients in the CLL4 trial has been documented.[8] Patients with >20% deletion had refractory disease with only 1/22 of such patients achieving a nodal partial remission and 40% surviving at 2 years. Few authors have probed relative responses to alemtuzumab in CLL patients according to p53 deletions and/or mutations (Table 2).[4,6,9] We add to these data, highlighting the efficacy of alemtuzumab in refractory CLL irrespective of p53 deletion. Overall responses, as well as responses among patients with p53 deletions in our series, were comparable to those in other reports.

Although none of the patients harboring p53 deletions achieved complete remission, such patients did eliminate all demonstrable CLL, falling short of complete remission only because of cytopenia(s). Lozanski *et al.*[4] described similar cases of patients who approached, but did not attain complete remission.

Fludarabine may facilitate p53-mutant, multi-drug resistant, CLL clones associated with an aggressive course.[10] This potential predilection, in conjunction with the dose-dependent behavior of p53 deletional status and superior responses to first line versus second line fludarabine treatment,[2] emphasizes the need to target therapy pre-emptively in patients with p53 deletions. Treatment with alemtuzumab should ideally be initiated earlier in the disease, before multiple therapies and/or advanced stage. We report a representative summary of responses to alemtuzumab among patients harboring p53 abnormalities detected by FISH. Screening by FISH to identify such patients is important since this may define treatment choice; moreover, quantification of deletion may be prognostic.

A prospective review of alemtuzumab in treatment-naïve patients with and without p53 abnormalities may furnish robust evidence to direct clinical practice towards up-front, targeted alemtuzumab therapy for patients with p53 abnormalities, and allow maximum utility, and minimum toxicity from this agent. Concurrent or sequential high-dose methylprednisolone or fludarabine may be useful, particularly for bulky lymphadenopathy.

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