Treatment of relapsed Hairy cell leukaemia

2nd cycle of cladribine

“Data concerning second-line and subsequent treatments for HCL with purine analogs are scant. Reported series range from 5 to 59 evaluable patients at second-line therapy (total, 193 patients), with overall response rates (ORR) from 83% to 100% and complete response (CR) rates from 52% to 89%,from 2 to 9 patients at third-line therapy (total, 20 patients), with a combined ORR of 85% and a combined CR rate of 55%. Recurrence rates and PFS from those series were reported variously and cannot be compared” (taken from Else et al[1]).

TABLE 1
Results From the Royal Marsden National Health Service Trust/Institute of Cancer Research Series Using the Standard Treatment (Pentostatin or Cladribine) as a Single Agent*

Variable	Summary result
Results of retreatment with the alternative purine analog after nonresponse to first-line purine analog therapy (5 patients)	
ORR	100%
CR	60%
Results of second-line therapy (73 patients, including the above)	
ORR	98%
CR	70%
Median PFS	90 mo
Recurrence at 2 y	15%
Recurrence at 3 y	20%
Recurrence at 5 y	40%
Results of third-line therapy (20 patients)	
ORR	100%
CR	45%
Median PFS	49 mo
Recurrence at 2 y	33%
Recurrence at 3 y	40%
Recurrence at 5 y	70%
Results of all retreatments at second- and third-line therapy	
Proportion of responses equivalent or superior to previous line of therapy (n = 70 assessable patients)	81%

ORR indicates overall response rate; CR, complete response; PFS, progression-free survival.
* See Else et al., 2005.[5]

Rituximab

Zenhausern et al[2] reported 26 patients previously treated with 2-CdA treated with rituximab 375 mg/m^2 day 1, 8, 15, 22. ORR was 80%, CR in 32%. Remission duration was median 33.6 months.

Nieva et al from the Scripps Clinic[3] reported 24 patients with relapsed HCL treated with rituximab 375 mg/m^2 day 1, 8, 15, 22. Of the pts, 3 (13%) achieved complete remissions and 3 (13%), partial responses. Thus, 6 (25%) of 24 pts achieved a response following rituximab.

Hagberg and Lundholm[4] treated 11 HCL patients (eight relapsing and three newly diagnosed) with rituximab, in a dose of 375 mg/m^2 once a week for 4 weeks. The response rate was seven out of eleven (64%) with six complete remissions and one partial remission, all which have lasted between 0 and 34 months (median 14 months).

Angelopoulou et al [5] from Buffalo, NY retrospectively analysed 12 patients treated with rituximab from a total of 110 patients seen between 1980 and 2006. 7 patients were previously treated with IFN only. Rituximab was given in a dose of 375 mg/m^2 once a week for 6 weeks. Four patients achieved CR (33%), while another 4 PR, for an overall response rate of 67%. Three out of 4 PRs showed a complete restoration of their blood counts. Thus 7/12 patients recovered normal blood counts completely. All CRs had a complete immunophenotypic response, while all PRs displayed residual disease. Three patients (28%)

were resistant to Rituximab and another withdrew early after the 1st Rituximab infusion due to severe thrombocytopenia. All 4 complete responders are alive off treatment without evidence of disease at a median follow-up of 13 months (range: 7–17). Among the 4 partial responders, one remains in PR with normal blood counts at 46 months. The remaining 3 patients were retreated with Rituximab at 6, 10 and 31 months, and all three achieved a response. Splenomegaly and more extensive bone marrow infiltration prior to Rituximab administration tended to be associated with lower response rates.

Thomas et al [6] at MDACC reported fifteen patients with relapsed or primary refractory HCL after nucleoside analogs received rituximab 375 mg/m^2 weekly for a total of 8 planned doses. An additional 4 doses could be administered to responders who had not achieved complete response (CR). The overall response rate was 80%. Eight patients (53%) achieved CR, 2 (13%) attained CR by hematologic parameters with residual marrow disease (1% to 5% marrow hairy cells), and 2 (13%) had a partial response. Of the 12 responders followed for a median of 32 months (range, 8 to 45+ months), 5 patients (42%) had progression of disease 8, 12, 18, 23, and 39 months from the start of therapy. Three patients failed to respond (after 4, 6, or 8 doses).

Cladribine and rituximab

Cervetti et al[7] treated 27 patients with HCL in PR or MRD+ after cladribine. ORR to cladribine was 89% (CR 26%). Patients received rituximab 375 mg/m^2 once a week for 4 weeks starting at a median 4 months post cladribine. ORR increased to 100% (CR 89%) at 2 months post rituximab. 70% became MRD negative which persistted in all patients at a median follow up of 36 months. 5 year PFS was 83%. PFS was improved in patients achieving CR (2-year PFS 50% for patients achieving PR vs. 94% for cases in CR) and MRD negative (30% in cases MRD-positive vs. 100% for patients MRD-negative).

Else et al [1] from the Marsden conducted a retrospective review of 8 patients who received pentostatin or cladribine combined concurrently (n = 6 patients) or sequentially (n = 2 patients) with rituximab at second-line therapy (n = 3 patients) and at subsequent lines of therapy (n = 5 patients). Results from a previously reported database of 219 patients with HCL (73 patients who received second-line therapy and 20 patients who received third-line therapy) were used as a historic control group against which to measure benefit. All 8 patients responded to therapy, with 7 complete responses (CRs) (87.5%) and minimal toxicity. All patients who had CRs were negative for minimal residual disease (MRD). At a median follow-up of 29 months (range, 5-39 months) 1 patient developed recurrent disease, and the estimated 2-year recurrence rate was 20% (0% after second-line therapy and 25% after subsequent lines of therapy). In the historic control group, the CR rates were 70% after second-line therapy and 45% after third-line therapy, and the recurrence rates at 2 years were 15% and 33%, respectively. The combination of purine analogs with rituximab suggested an added benefit compared with standard treatment.

These data were summarised in a recent paper reviewing the cohort at a median 16 years follow up.[8]

	Single agent pentostatin or cladribine			Combined with rituximab
	First line $n = 233$	Second line $n = 84$	Third line $n = 23$	(2nd, 3rd, 4th or 6th line) $n = 12$
Overall response rate	97%	97%	100%	100%
Complete response rate	80%	69%	50%	92%
Proportion of responses equivalent or superior to previous line of therapy	N/A	82%	87·5%	100%
Median progression-free survival in years*	10·5	9	6·5	5+ (not reached)
Median relapse-free survival in years*	16	11	6·5	5+ (not reached)

*Includes non-responders.

References

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