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### Authors

Chihara, Dai
Kantarjian, Hagop
O'Brien, Susan
et al.



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# Long-term durable remission by cladribine followed by rituximab in patients with hairy cell leukaemia: update of a phase II trial

**Dai Chihara**[1], **Hagop Kantarjian**[1], **Susan O'Brien**[1], **Jeffry Jorgensen**[2], **Sherry Pierce**[1], **Stefan Faderl**[1], **Alessandra Ferrajoli**[1], **Poku Rebecca**[1], **Preetesh Jain**[1], **Phillip Thompson**[1], **Mark Brandt**[1], **Rajyalakshmi Luthra**[2], **Jan Burger**[1], **Michael Keating**[1], and **Farhad Ravandi**[1]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

[2]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

## Summary

Nucleoside analogues are highly active in patients with hairy cell leukaemia (HCL); however, patients continue to relapse. This phase II study evaluated the efficacy and safety of cladribine followed by rituximab in patients with untreated HCL (N=59), relapsed HCL (N=14) and HCL variant (HCLv, N=7). Cladribine 5.6 mg/m$^2$ was given intravenously (IV) daily for 5 days and was followed approximately 1 month later with rituximab 375 mg/m$^2$ IV weekly for 8 weeks. Complete response rate in patients with untreated HCL, relapsed HCL and HCLv was 100%, 100% and 86%, respectively. With a median follow up of 60 months, 5-year failure-free survival (FFS) in patients with untreated HCL, relapsed HCL and HCLv was 95%, 100% and 64%, respectively. Median duration of response to the cladribine followed by rituximab was significantly longer than the first-line cladribine single agent in patients who received this treatment as second-line treatment (72 months vs not reached, P=0.004). Almost all patients (94%) achieved negative minimal residual disease (MRD) after the treatment. Positive MRD during the follow up did not necessarily result in clinically relevant relapse. Cladribine followed by rituximab is highly effective even in patients with relapsed disease and HCLv, and can achieve durable remission.

### Keywords

Hairy cell leukaemia; cladribine; rituximab; phase II study

Corresponding author: Farhad Ravandi, Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, fravandi@mdanderson.org, Phone: 713-745-0394, Fax: 713-794-4297.

**Author contributions**

F.R. and H.K. designed the study. S.O., J.J., S.P., S.F., A.F., P.R., P.J., P.T., M.B., R.L., J.B. and M.K. provided the data and contributed to patient care. D.C. performed statistical analysis. D.C. and F.R. interpreted the data and wrote the paper. All authors have read and approved the final version of the manuscript.

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None

## Introduction

Hairy cell leukaemia (HCL) is a rare indolent mature B-cell neoplasm, accounting for only 2% of lymphoid leukaemias (Swerdlow, *et al* 2008). The majority of patients have the *BRAF* V600E mutation (Tiacci, *et al* 2011), which leads to Ras-independent activation of the MAPK pathway, causing hyper-activation of *ERK*, therefore promoting the proliferation and survival of HCL cells (Tiacci, *et al* 2013).

The nucleoside analogues cladribine and pentostatin are highly active as monotherapy for HCL, with complete response (CR) rates of 80 to 90% (Kraut, *et al* 1989, Piro, *et al* 1990), however, patients continue to relapse with median response duration of 8 to 10 years, and there seems to be no plateau in the disease-free survival curves of these studies (Flinn, *et al* 2000, Goodman, *et al* 2003). Re-treatment with same nucleoside analogue is also effective, but the CR rate and response duration following subsequent courses tend to be lower and shorter (Else, *et al* 2009, Goodman, *et al* 2003, Zinzani, *et al* 2010). As the median age at HCL diagnosis is 50–55 years, new effective strategies beyond purine analogue monotherapy are needed to extend response duration and eliminate relapse. Previous studies have demonstrated that deeper response to therapy will result in longer response duration (Else, *et al* 2009, Goodman, *et al* 2003), raising the question of whether achieving negative minimal residual disease (MRD) status (Ravandi, *et al* 2006) after the initial therapy would be a surrogate for achieving long-term remission.

HCL variant (HCLv) has a distinct immunophenotype, such as absence of CD25 and annexin-1. HCLv is biologically different from HCL and accounts for only 10% of cases, occurring more frequently in the elderly with a median age at diagnosis of around 70 years. Furthermore, patients with HCLv are less responsive to purine analogues with CR rates reported to be around 50% (Matutes, *et al* 2003). Overall, patients with HCLv have shorter survival (Robak 2006) and more effective treatments are also needed for this disease.

The aim of this phase II study was to demonstrate the efficacy of chemo-immunotherapy, cladribine followed by rituximab, in patients with HCL including HCLv. Rituximab is effective in HCL as single agent and can synergistically potentiate the apoptotic effects of cladribine (Chow, *et al* 2002, Thomas, *et al* 2003). Studies in other lymphoid neoplasms have shown that rituximab can be combined safely and effectively with chemotherapy. We previously reported the results of this strategy in 36 patients with newly diagnosed HCL (31 HCL, 5 HCLv) who participated in this trial (Ravandi, *et al* 2011). Here, we report an update of this phase II trial, including the cohort of patients in first relapse also treated, as a subset, on the study.

## Patients and Methods

### Patients

Patients were eligible if they had newly diagnosed or first relapsed HCL with active disease requiring therapy as per standard criteria. Patients were also eligible to participate if they had HCLv. The diagnosis of HCL and HCLv was established according to the WHO classification (Jaffe, *et al* 2001, Swerdlow, *et al* 2008). A total of 83 consecutive patients

with newly diagnosed (N=59), first relapsed HCL (N=14) or HCLv (N=7) were enrolled in this prospective trial between June 2004 and February 2015. Three patients did not receive rituximab because of patient's choice (N=2) or insurance issues (N=1) and were excluded from the analysis. Thus, a total of 80 patients were analysed in this update.

The detailed treatment regimen, response criteria, and assessment of MRD and *IGHV* mutation status were described previously (Ravandi, *et al* 2011). Briefly, cladribine 5.6 mg/m$^2$ was given intravenously over 2 h daily for 5 days, followed by 8 weekly doses of rituximab 375 mg/m$^2$ starting 28 days (+/−4 days) after the initiation of cladribine. We chose to administer rituximab sequentially as a caution, as at the time there was no specific literature regarding the safety of concurrent therapy. Response was assessed at day 28 (+/−4 days: prior to rituximab) and after completion of rituximab. MRD was assessed by multiparameter flow cytometry (FCM) at the time of response evaluation (Ravandi, *et al* 2011). The limit of detection of MRD by FCM was 0.02%.

### Statistical analysis

The Fisher exact tests were used for the descriptive statistical analyses on categorical variables and ANOVA for continuous variables. Failure-free survival (FFS) was defined as the time from initiation of therapy to change of treatment, clinical relapse of the disease (excluding MRD relapse without pathologically proven HCL or symptoms) or death from HCL. Overall survival (OS) was defined as the time from commencement of treatment to death from any cause. FFS and OS curves were constructed using the Kaplan-Meier method (Kaplan and Meier 1958), and groups were compared using the log-rank test. The patients were split into three groups [newly diagnosed HCL (untreated), relapsed HCL (relapsed) and HCLv] and analysed separately. Cumulative incidence of second primary malignancies was calculated by competing risk regression analysis as described elsewhere in detail (Gooley, *et al* 1999). In this analysis, death without secondary malignancies was defined as the competing event. All analyses were performed using STATA version 13.1 (StataCorp LP, College Station, TX), with the significance level set at 5%.

## Results

### Patient characteristics

Baseline patient characteristics are summarized in Table I. The median age at study enrolment was 55 (range: 31–91) years in the untreated cohort, 47 (range: 32–76) years in the relapsed cohort and 71 (range: 50–89) years in the HCLv cohort. HCLv patients were significantly older, had significantly higher white blood cell counts and splenomegaly, and higher platelet counts. The median follow up duration for all patients was 60.2 months (range: 8.9–134.8 months).

### Untreated cohort

Overall, 59 patients received cladribine followed by rituximab as their first line treatment. CR rate was 100%. Two patients required subsequent treatment. One patient experienced relapse 12 months after treatment with 50% bone marrow involvement but remained clinically stable for a long period of time, starting second line treatment with ibrutinib 42

months after relapse. One patient received rituximab single agent for MRD recurrence (having achieved prior negative MRD) but without morphological evidence of HCL in the bone marrow, 52 months following the first line treatment. Only one patient in this cohort died, and the cause of death was metastatic esophageal adenocarcinoma. 5-year FFS and OS was 94.8% (95% confidence interval [CI]: 79.6–98.8%) and 96.8% (95%CI: 79.2–99.5%), respectively (Figure 1).

### Relapsed cohort

Overall, 14 patients received cladribine followed by rituximab for relapsed disease. All patients received protocol treatment as the second line treatment. First line treatment for these patients included: cladribine alone in 12 patients, pentostatin alone in one patient and rituximab monotherapy in one patient. CR rate for the protocol treatment was 100%, and the 5-year FFS and OS were 100% (Figure 1). Among the patients with prior cladribine monotherapy, the median duration of response to first line cladribine was 72.1 months (95%CI: 16.3–108.9 months). There was a statistically significant difference in FFS between the first line cladribine monotherapy and the second line treatment with cladribine followed by rituximab (Figure 2, P=0.004).

### Hairy cell-variant

Overall, 7 HCLv patients received cladribine followed by rituximab, all as first line treatment. CR rate was 86% (95%CI: 42–100%). Two patients experienced relapse (19 and 96 months after initiation of therapy); one was re-treated with cladribine followed by rituximab and one is under observation mainly due to her advanced age (99 years old). One patient underwent splenectomy after failing initial therapy with cladribine and rituximab because of persistent splenomegaly and lack of achievement of CR. Three patients died, one from metastatic pancreatic cancer, one from metastatic lung cancer and one (the patient who received re-treatment) from progressive HCLv. 5-year FFS and OS was 64.3% (95%CI: 15.2–90.2%) and 51.4% (95%CI: 11.8–81.3%), respectively (Figure 1).

### *IGHV* gene status

A total of 34 patients (23 untreated, 5 relapsed, 6 HCLv) were evaluable for *IGHV* gene mutation status . Among them, 11 patients had unmutated *IGHV* (5 untreated, 3 relapsed, 3 HCLv). None of the patients with HCL (untreated or relapsed) with unmutated *IGHV* have relapsed at the time of data analyses. Two patients with HCLv and unmutated *IGHV* have relapsed at 4 and 19 months with the other patient dying from pancreatic cancer. Two HCLv patients with mutated *IGHV* are still alive and progression-free at 15 and 80 months with the third relapsing at 96 months (p=0.09).

### Assessment of minimal residual disease

Eleven patients (14%) achieved MRD negative disease after cladribine alone; all of these patients were in the untreated group (11/59 patients; 19%), while no patients with relapsed disease or HCLv achieved negative MRD after cladribine monotherapy. This difference was not statistically significant, probably due to the limited number of patients (P=0.134). Following rituximab, 59 patients (74%), including 76% of the untreated patients, 64% of the

relapsed patients, and 71% of HCLv patients, achieved a negative MRD status; this difference was not statistically significant (P=0.69). The initial two response assessments at approximately one and three months post-initiation of therapy (after completion of cladribine and after completion of rituximab) were performed using a bone marrow aspirate and biopsy specimen. Subsequent MRD was assessed using peripheral blood specimens. An additional 16 patients eventually achieved negative MRD status assessed only in peripheral blood. Therefore, overall, 75 patients (94%) achieved a negative MRD status. The median time to achieving MRD negativity was 2.9 months (range: 0.8–18.9 months). Given that very few relapses, MRD negativity at any time during treatment was not significantly associated with longer FFS in patients with untreated, relapsed or HCLv (data not shown). Even the five patients in whom we could not confirm a negative MRD did not progress at the time of data analysis.

Six patients (4 untreated, 2 HCLv) had MRD recurrence after achieving negative MRD status; 4 of these patients required subsequent therapy but the other 2 patients had no clinically and pathologically relevant relapse and remain on observation at 24+ and 73+ months. The time from positive MRD to the next treatment in 4 patients was 0 (started next treatment due to positive MRD without clinically relevant disease), 1, 5 and 54 months.

### Toxicity and second primary malignancies

As reported previously (Ravandi, *et al* 2011), the regimen was well tolerated with no severe or unexpected toxicity. Non-haematological grade 3 toxicities were seen in 4 patients: fatigue (N=2), rash and hyperbilirubinaemia (both N=1). There was no grade 4 non-haematological toxicity. Nineteen patients had reversible grade 3 or 4 infections including febrile neutropenia, cellulitis and pneumonia.

Overall, 6 patients developed second primary malignancies (1 oesophageal cancer, 1 lung cancer, 1 pancreatic cancer, 1 basal cell carcinoma, 1 melanoma, 1 melanoma and chronic lymphocytic leukaemia). Interestingly, one patient has developed chronic lymphocytic leukaemia without the need for treatment, and remains under observation. The 5-year cumulative incidence of second primary malignancies was 8.7% (95%CI: 3.6–20.4%); no myelodysplastic syndrome (MDS) has been observed.

## Discussion

This update further confirms the very high CR rate with sequential cladribine followed by rituximab for patients with HCL, including those with relapsed disease, a group with the expectation of a CR rate of around 70% using cladribine monotherapy (Else, *et al* 2009, Goodman, *et al* 2003, Zinzani, *et al* 2010). Responses were durable and only two patients required subsequent treatment, although the median follow-up duration of 60 months remains relatively short. Of note, among the patients treated for first relapse, none has experienced a second relapse. The median duration of response to second line cladribine monotherapy has been reported to be around three years (Goodman, *et al* 2003, Zinzani, *et al* 2010). In the current study, none of the patients treated second line has relapsed with a median follow-up of 60 months, suggesting the superiority of the combination strategy particularly in the relapsed setting. The difference in the FFS between first line cladribine

and second line cladribine plus rituximab was statistically significant (Figure 2). Else et al (2015) also reported similar results in 26 patients who received a purine analogue combined with rituximab for relapsed disease following purine analogue monotherapy Relapse-free survival was significantly longer with combination treatment (Hazard ratio: 0.10; 95%CI: 0.03–0.32). Our results are further suggestive of the efficacy of chemo-immunotherapy, as also shown by others (Cervetti, *et al* 2008, Else, *et al* 2015, Leclerc, *et al* 2015). Several recently published guidelines recommend combined chemo-immunotherapy with rituximab for second line treatment, or for patients who could not achieve CR after first line purine analogue monotherapy (Cornet, *et al* 2014a, Jones, *et al* 2012, Robak, *et al* 2015). Our result also indicates the high efficacy of chemo-immunotherapy for first line treatment. However, given that a high proportion of patients with newly diagnosed HCL do extremely well with purine analogues alone, well-designed trials are needed to determine whether chemo-immunotherapy is associated with a longer relapse-free survival, and even OS, than single-agent nucleoside analogues. Longer follow up is needed to confirm the long-term treatment-free survival and to detect patients at high risk for relapse.

The achievement of CR compared to PR has been shown to be associated with achieving a longer FFS (Dearden, *et al* 2011, Goodman, *et al* 2003, Rosenberg, *et al* 2014). This raises the question of whether eradication of MRD after the initial treatment can be associated with further prolongation of FFS and potential cure. In the current study, the proportion of patients achieving a negative MRD status increased after the administration of rituximab. However, clearance of bone marrow disease is often delayed after purine analogue therapy so it is not clear if this improvement of MRD status can be attributed entirely to the administration of rituximab. Furthermore, current guidelines recommend response assessment at 4–6 months after the end of treatment (Cornet, *et al* 2014a, Jones, *et al* 2012, Robak, *et al* 2015). Given that almost all patients achieved negative MRD at some point and there have been very few relapses, it is difficult to determine the utility of MRD assessment for predicting relapse and long-term FFS. Furthermore, six patients had MRD recurrence after having achieved a negative MRD status, 3 of who had no clinically relevant relapse requiring treatment for more than 2 years. This is consistent with previous studies, showing that patients with MRD can live many years without manifesting clinically relevant relapse (Sigal, *et al* 2010, Tallman, *et al* 1999). Investigators at the National Cancer Institute are conducting a phase II trial analysing the timing and effectiveness of rituximab in eradicating the MRD after cladribine (ClinicalTrials.gov Identifier: NCT00923013) (Arons, *et al* 2014). Patients are randomized to either receive cladribine alone or cladribine immediately followed by rituximab. Patients with positive MRD in peripheral blood at least 6 months after cladribine receive delayed rituximab. The study is on-going but preliminary results suggest that the combination strategy achieves a significantly higher rate of negative MRD than cladribine alone after 6 months (97% vs 32%, $p<0.001$). Furthermore, delayed rituximab cleared MRD in 75% of patients who had positive MRD at 6 months. Longer follow up is needed to determine if there is any difference in FFS by the timing of rituximab, and if the eradication of MRD is associated with longer FFS.

Consistent with a prior report (Kreitman, *et al* 2013), in this study, the combination of cladribine with rituximab was active for HCLv patients (CR rate: 86%) who are known to be more resistant to cladribine monotherapy. Patients with HCLv have shorter survival

(Matutes, *et al* 2003). In a recently published report from the investigators at Memorial Sloan Kettering, HCLv patients had shorter time to next treatment than the patients with classical HCL but had a similar OS (Getta, *et al* 2015), although the median follow-up duration was relatively short (47 months).

Several high-risk features, such as the presence of unmutated *IGHV* and *IGHV4-34*, are reported to be associated with a shorter response duration to nucleoside analogues (Arons, *et al* 2009, Forconi, *et al* 2009). The majority of patients (85–90%) have mutated *IGHV* (Forconi, *et al* 2009, Thorselius, *et al* 2005). However, patients with unmutated *IGHV* have a significantly shorter event-free survival compared to those with mutated *IGHV* (7.5 months vs not reached) (Forconi, *et al* 2009). In the current study, however, none of the HCL patients with unmutated *IGHV* experienced relapse. Chemo-immunotherapy may overcome this adverse factor and we propose that this group of patients may be particularly suitable for initial chemo-immunotherapy.

Recently, Rosenberg et al (2014) reported the results of very long-term follow-up (251 months) of young patients with HCL. Of the 88 patients studied, eight (9%) developed second malignancies. In another large retrospective study (N=487), 48 patients (10%) developed secondary malignancies after a median follow up of five years (Cornet, *et al* 2014b). Prior reports have suggested that the incidence of second malignancies in patients with HCL is not significantly different from that in the general population (Else, *et al* 2005, Rosenberg, *et al* 2014). Others have reported it to be significantly higher (Cornet, *et al* 2014b), and the subject remains controversial. In the current study, the incidence of second malignancies was similar to other prior reports (5-year: 8.7%). As expected, we did not observe an increased incidence of second malignancies or fatal infections after adding rituximab.

In conclusion, cladribine followed by rituximab is highly active and is associated with durable responses in patients with HCL. This strategy is highly effective even for patients who relapse following cladribine monotherapy. Specific subsets of patients, known to be less responsive to nucleoside analogues alone, including those with HCLv and those with unmutated *IGHV,* may particularly benefit from this strategy. Whether the efficacy of this strategy can be further increased by concomitant rather than sequential administration of rituximab (as has been see in other lymphoid neoplasms) and whether more novel CD20-directed monoclonal antibodies may have a role should also be established prospectively. These will probably need large, multi-national collaborative efforts in the future.

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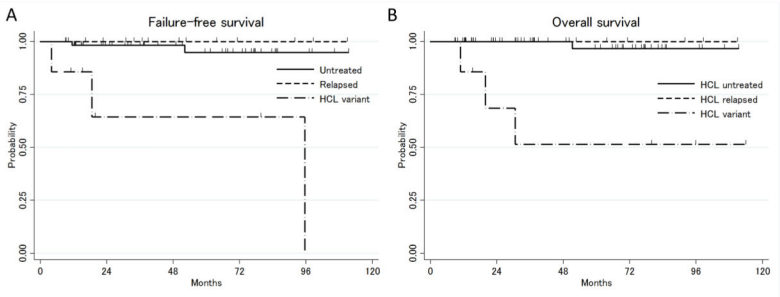


**Figure 1.**

Failure-free survival and overall survival of the study cohort

A; Failure-free survival, B; Overall survival.

HCL, Hairy cell leukaemia

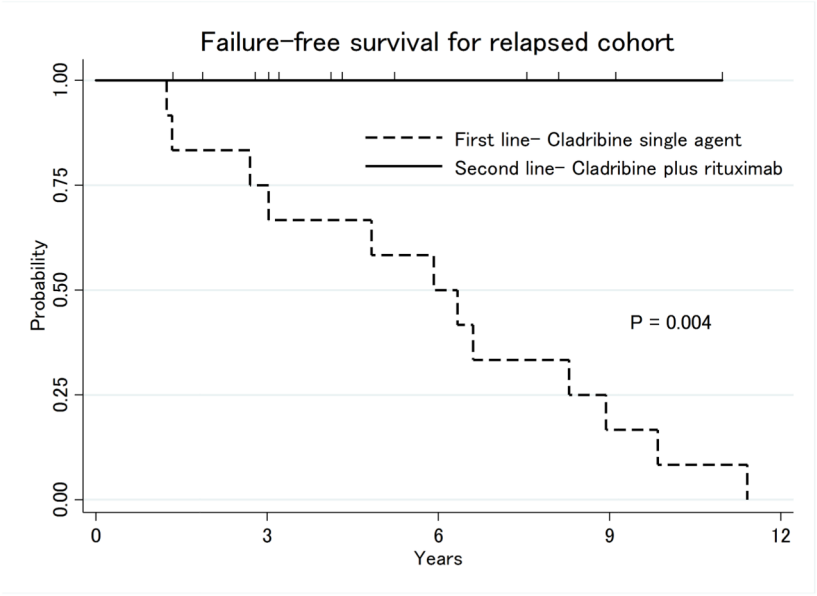


**Figure 2.**

Failure-free survival in relapsed patients who received cladribine single agent as first line treatment

**Table I**

Patient characteristics

| Characteristics | | Untreated | Relapsed | HCL variant | p-value |
|---|---|---|---|---|---|
| N | | 59 | 14 | 7 | |
| Median age (years) | (range) | 55 (31–91) | 47 (32–76) | 71 (50–89) | 0.003 |
| Male | n (%) | 46 (78) | 13 (93) | 5 (71) | 0.383 |
| WBC count (x$10^9$/l) | Median (range) | 2.7 (0.5–12.8) | 2.5 (1.5–6.9) | 31.6 (4.0–74.1) | <0.001 |
| Haemoglobin (g/l) | Median (range) | 124 (81–159) | 137 (83–163) | 126 (93–148) | 0.029 |
| Platelet count (x$10^9$/l) | Median (range) | 76 (35–206) | 96 (39–180) | 119 (91–275) | 0.001 |
| Bone marrow HCL (%) | Median (range) | 46 (8–95) | 22 (8–80) | 38 (14–81) | 0.101 |
| Splenomegaly, BCM (cm) | Median (range) | 0 (0–15) | 0 (0–10) | 4 (0–25) | 0.005 |
| *IGHV* mutated | n (%) | 18 (78) | 2 (40) | 3 (50) | 0.151 |

Abbreviations: HCL, hairy cell leukaemia; WBC, white blood cell; *IGHV,* immunoglobulin variable region heavy chain gene; BCM, below costal margin