Long-term follow-up after purine analogue therapy in hairy cell leukaemia

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A B S T R A C T

Since 2006 when we last reviewed the literature concerning the use of purine analogues in hairy cell leukaemia (HCL), results from several new and updated series have been published. Here we examine these reports and consider their implications for patient management. The two purine analogues pentostatin and cladribine remain the first-line treatments of choice for all patients with HCL. Although they have not been compared in randomised trials, they appear to be equally effective. A complete response is important for the long-term outcome and we look at how best this can be achieved. Evidence is emerging which supports the use of either purine analogue plus an anti-CD20 monoclonal antibody after relapse, though questions remain concerning the scheduling of the monoclonal antibody. Patients refractory to the purine analogues may require alternative agents.

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Introduction

The treatment of hairy cell leukaemia (HCL) with purine analogues is one of the greatest successes in the history of cancer treatment. From 1958, when Bouroncle et al. [1] first described the disease,

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until the early 1980s, median overall survival was around 4 years [2]. In contrast, many patients who were among the first to be given pentostatin (Nipent, Supergen, Dublin, CA, USA) [2–8], or cladribine (Leustatin, Ortho-Biotech, Bridgewater, NJ, USA) [9–14], are still alive 30 years later. Many are still in their first remission 15 years and more after treatment [15,16]. Long-term survival cannot be taken for granted, however. It is the result of careful patient management, from first-line treatment onwards.

There have been a number of developments of relevance to purine analogue treatment since our last review of the literature in 2006 [17]. In particular, longer follow-up is available, enabling the long-term assessment of outcomes after initial pentostatin or cladribine and the evaluation of these agents when used at second and subsequent lines of therapy [15,18,19]; the combination of a purine analogue with rituximab (MabThera, Roche Products Ltd, Hertfordshire, UK) has been evaluated for the treatment of relapsed HCL [20–22]; a number of new agents have become available for non-responders to purine analogues, or for patients requiring salvage therapy (see the chapters by Kreitmann, Zenz and Forconi in this issue); cladribine for subcutaneous administration (LITAK, Lipomed Gmbh, Weil am Rhein, Germany) has been widely introduced [23,24]; there is a move towards improving the long-term outcome by converting a partial response (PR) to a complete response (CR) [15,25]; and evidence-based guidelines have recently been published [25–27]. The purpose of this review is to provide an update of the available literature and of developments in our own large series. In the second section we discuss the implications of these findings for the treatment and management of patients receiving a purine analogue.

Updated results from the published series

First line purine analogue treatment

Responses to first-line treatment

Earlier retrospective studies of pentostatin and cladribine reported overall response rates (ORR) of more than 85% and CR rates of around 75%, with median relapse-free survival (RFS) up to 15 years (Supplementary Table S1) [28–36]. These results have been confirmed by recent studies, all retro-spective (Table 1), including long-term data from three earlier series: from the Scripps Clinic [37], from Bologna [18], and our own series, updated in 2009 [19], and reviewed in 2011 with a focus on the implications for clinical practice [15]. There are also two series, from Spain and France, with some minor overlap of patients from previous reports [38,39] and three new reports from Turkey, India and Mexico [40–42]. Four of these studies report results with both cladribine and pentostatin, while the other four report only cladribine.

In all eight recent studies the ORR was >95% and the CR rate >75%. Three large series which included both agents, from France, Spain and the UK, found no difference in ORR or CR rates between pentostatin and cladribine [19,38,39]. The Italian series included both agents, but did not analyse the results separately [18]. Rosenberg et al. [37] focused on 88 younger cladribine-treated patients from the Scripps Clinic, aged ≤40 years, and reported 100% ORR and 88% CR. In the other three cladribine series [40–42] the ORR and CR rates were in line with those from countries with a more established history of purine analogue treatment. In India, 27 of 35 patients diagnosed with HCL received cladribine, while 8 did not, due to financial constraints [41]. In two institutions in Mexico the CR rate with cladribine was 100%; however, only 11/29 patients were able to obtain cladribine and the remainder received inter-feron [42]. The lack of availability and affordability of cladribine in those countries is a concern.

As in other earlier reported series [13,35], 18 patients treated with cladribine in our series (12 at first line and 6 at second line), who remained in PR at the 4–6 month bone marrow (BM) evaluation, received a repeated cycle 4–7 months after the first cycle. This led to a CR in 14 patients (78%) [15]. Similarly, in the Spanish series 8 patients in PR were treated with a second cycle of cladribine, which led to a CR in 6 patients (75%) [38]. In the Indian series 2 patients received a second cycle of treatment at 6–8 months and both achieved a CR [41].

Relapse rates

The earlier retrospective studies with 2–5 years median follow-up reported relapses after pen-tostatin or cladribine in between 10% and 20% [4,12,13], with higher relapse rates in patients who only

Table 1

Outcomes after purine analogue treatment: results from the recently published series.

Study centre	Authors & date	Purine analogue	No. eval. patients	1st line ORR %	1st line CR %	Median FU (months)	Relapsed % (after CR/PR)	No. eval. 2nd line patients	2nd line ORR %	2nd line CR%	2nd relapse % (after CR/PR)	% 2nd malignancies
Scripps Clinic USA[a] (pts aged ≤40 y only)	Rosenberg et al., 2014 [37]	Cladribine	83	100	88	251	51 (CR) 80 (PR)	27	96	44	–	9 (after)
Bologna, Italy[e,a]	Zinzani et al., 2010 [18]	Pentostatin	10	96	77	105	44	5	88.5	73.5	64	–
		Cladribine	75				41					
Royal Marsden Hospital UK[a,b]	Else et al., 2009 [19]	Pentostatin	188	96	82	172	44	26[d]	97	69[c]	(median RFS 129 m)	1 (before)
		Cladribine	45	100	76[c]	108	38	58[d]				12 (after)
Spain (GELLC)[a]	Lopez et al., 2014 [38]	Pentostatin	27	100	92	145	51	–	–	–	–	–
		Cladribine	80	100	88[c]	63	25	–	–	–	–	–
France multicentre[a]	Cornet et al., 2014 [39]	Pentostatin	99	99	82	58	23	28[d]	–	–	(median RFS 153 m)	8 (before)
		Cladribine	281	100	83	53	18	59[d]	–	–	(median RFS 79 m)	10 (after)
Turkey multicentre	Hacioglu et al., 2015 [40]	Cladribine	78	97	81	28	16 (CR) 23 (PR)	19	100	68	31.5	3 (before) 1 (after)
New Delhi, India	Somasundaram et al., 2014 [41]	Cladribine	27	100	100[c]	26	18 (CR)	5	100	100[c]	0	0
Mexico	Ruiz-Delgado et al., 2012 [42]	Cladribine	11	100	100	25	27 (CR)	3	–	–	–	–

Abbreviations: eval. − evaluable; FU − follow-up; CR − complete response; PR − partial response; RFS − relapse-free survival; GELLC − Spanish Cooperative Group on CLL. A dash (−) denotes no information given. 'Before' and 'after' denote diagnosis of second malignancies before or after purine analogue treatment.

[a] Includes some results from a previous series, successively followed up with increased recruitment.

[b] Some analyses were further updated in 2011 [15].

[c] After a second course of cladribine in some patients.

[d] Some patients were switched to the alternative purine analogue.

[e] The results include a further 33 patients treated with interferon and 3 with splenectomy.

attained a PR compared to those who obtained a CR (Supplementary Table S1). In the earlier studies with longer follow-up, relapse rates after a CR were 14%–46% with pentostatin, at 5–11 years median follow-up [7,28,29,32,36] and 27%–37% with cladribine, at 7–10 years median follow-up [31,33–36]. Reported relapse rates after a PR were 21% at 5 years and 73% at 11 years (pentostatin) [32,36] and 50%–100% (cladribine) [31,33,35,36]. Goodman et al. [31] reported a median time to first relapse of 44 months after a CR versus 31 months after a PR (p < 0.0005). Two other series also reported longer median times to first relapse in patients in CR (35, 56 months) versus PR (10, 12 months) [32,35].

The recent studies with short median follow-up (2–5 years) reported relapses in 17%–27% (Table 1) [39–42]. The Turkish study reported a median time to relapse of 36 months after a CR versus 6 months after a PR [40]. In the recent studies with longer follow-up, relapse rates after pentostatin were 44% at 14 years median follow-up [19] and 51% at 12 years [38]. After cladribine the relapse rates were 25% at 5 years, rising to 54% at 21 years [18,19,37,38]. The Scripps Clinic reported a 51% relapse rate after a CR versus 80% after a PR, with a median time to relapse of 57 months after a CR and 20 months after a PR [37].

These results indicate a general pattern of relapses occurring in about half of patients in the long term, while the rest remain in indefinite remission, suggesting purine analogues may have a curative potential. Relapses tend to occur in the early years after treatment, with around a quarter of patients in CR relapsing in the first 5 years. Results after a PR are less encouraging, with higher rates of early relapse and up to 100% relapsing in the longer term. Our study reported a relapse rate of 24% with pentostatin and 34% with cladribine at 5 years, 42% with both agents at 10 years, and 47%–48% respectively at 15 years [19], demonstrating a declining proportion of patients relapsing in the later years. We found that patients still in CR at 5 years had only a 25% risk of relapse by 15 years. Of the 14 patients who achieved a CR after a repeated cycle of cladribine, all but one remained in remission at a median follow-up of 6 (range 1–16) years [15]. The Spanish study reported that 34% of patients given pentostatin and 23% given cladribine required further treatment by 5 years and 56% and 40% respectively by 10 years [38]. The time elapsing between first- and second-line treatment was not significantly different between the two agents, but it was longer in patients in CR (median 170 months) versus those in PR (median 44 months; p < 0.001).
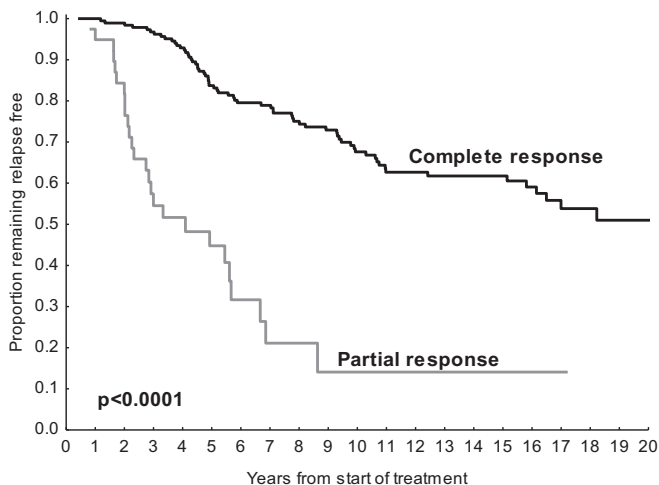

Fig. 1. Relapse-free survival (RFS) by response to first-line single-agent treatment with either pentostatin or cladribine, showing a significant difference between patients achieving a complete response (CR) versus a partial response (PR). The median RFS was 16 years overall: 20 + years (not reached) for patients attaining a CR and 4 years after a PR (log-rank p < 0.0001). There was no difference in RFS by type of treatment (pentostatin or cladribine). Reprinted from: Dearden et al.; Leuk Lymphoma. 2011; 52 Suppl 2: 21–24 [15].

Relapse-free survival

Median RFS (censored at the latest follow-up date in patients remaining disease-free) was a little over 13 years in the French series [39] and 16 years in our series [15], with equivalent results for pentostatin and cladribine in both series. In our series the median RFS for patients in CR was over 20 years (not reached) but only 5 years for those in PR (p < 0.0001; Fig. 1) [15].

Salvage treatment with purine analogues

Outcomes after second and subsequent lines of purine analogue therapy

Several reports have included data concerning the use of purine analogues as salvage therapy, showing that these agents can still be effective as second- and third-line therapy in a majority of patients [15,18,31,32,35,37,40]. However, the CR rates tended to be lower at second line (Table 1) and lower again at third line [15,18,37,40]. The respective rates for the three lines of treatment were: 81%, 66% and 50% in our series [15], 88%, 44% and 20% at the Scripps Clinic [37] and 81%, 68% and 67% in the Turkish series [40]. Zinzani et al. [18] reported declining CR rates and response duration across 5 lines of treatment. From 1st line to 5th line respectively, the CR rates were 77%, 73.5%, 70.5%, 65% and 50%. The median response duration was 2.7, 2.5, 2.2, 1.6 and 1.3 years. Median response duration was also shorter with each course of treatment in other studies [18,19,31,35,39].

In the French series estimated median RFS after second-line treatment was significantly longer with pentostatin than cladribine (153 versus 79 months; log-rank p = 0.02; hazard ratio: 0.39; 95% confidence interval [CI]: 0.18—0.85) [39]. In our study a second-line CR (versus a PR) was the only factor significantly associated with longer second-line RFS (p < 0.0001). We found that RFS was shorter after each line of treatment, decreasing from 16, to 11, to 6.5 years, but the decrease was only seen in partial responders. Importantly, CRs, although progressively less readily attained, were equally durable, whether obtained with first, second or third-line therapy [19].

In the French series, no significant differences were observed in second-line CR rates or RFS between patients who received the same purine analogue again versus those who switched to the alternative [39]. Similarly, in our series the CR rate was 71% in patients retreated with the same agent and 68% in those who switched [36].

Outcomes after salvage with chemo-immunotherapy

After relapse, purine analogues combined with the anti-CD20 monoclonal antibody rituximab show good results [20—22,43]. CD20 expression is significantly higher in HCL than in other B-cell leukaemias [44] and rituximab, used as a single agent in HCL, has shown improved response rates by reducing the degree of BM infiltration. However, there is currently a lack of data from randomised trials to evaluate the efficacy of the combination relative to a purine analogue alone. Results with chemo-immunotherapy are described in full by Ravandi in this issue, but we include here a further analysis of our own series, last reported in 2011 [20] and now with increased follow-up and recruitment.

Twenty-six patients who relapsed after a median of 3 (range 1—6) previous lines of purine analogue therapy were treated with either pentostatin (n = 15) or cladribine (n = 11) combined with rituximab. Eighteen patients (69%) had already received the chosen purine analogue at one or more previous lines of therapy. Patients received between 4 and 8 (median 6.5) intravenous infusions of rituximab at 375 mg/m^2, concurrently with the purine analogue in 20 patients and sequentially in 6, starting 1—2 months after the completion of purine analogue therapy. Twenty-five patients were evaluable for response with an overall response rate of 96% and a CR rate of 88%. There was one PR and one patient had a good response without confirmation of CR. The only non-responder was successfully treated with vemurafenib and remained in remission 2½ years later. The patient in PR relapsed after 10 months and died two years later, after 3 further lines of treatment, with anti-CD25 and anti-CD22 antibodies, and fludarabine with cyclophosphamide. One patient in CR relapsed after 56 months and received vemurafenib, remaining in PR two years later. Both patients who relapsed had received only 4 infusions of rituximab.

At a median follow-up of 78 (range 3—136) months from the start of combination treatment, we compared the RFS of these 26 patients with their own first-line RFS after pentostatin or cladribine alone, using the Kaplan—Meier method. Patients remaining in remission were censored at 31st March
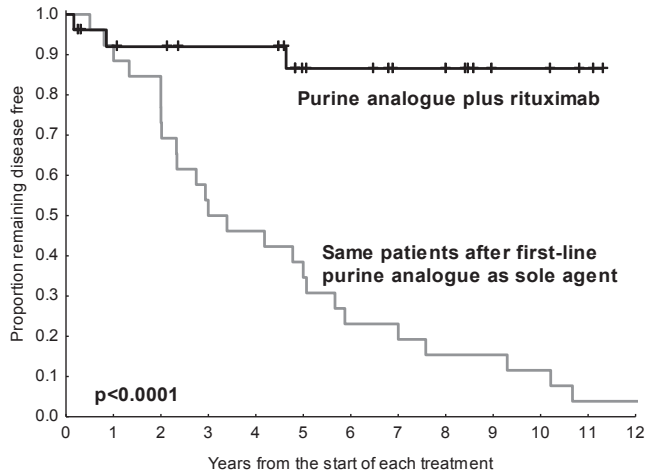
Fig. 2. Relapse-free survival (RFS) following treatment with the combination of a purine analogue plus rituximab compared with the RFS of these same 26 patients following their earlier first-line therapy with a purine analogue (cladribine or pentostatin) alone (log-rank p < 0.0001).

2015. Two patients from overseas were censored at the date of last known follow-up. RFS was significantly longer after combination treatment than after first-line treatment (hazard ratio: 0.10; 95% CI: 0.03–0.32; log-rank p < 0.0001; Fig. 2). After combination treatment, RFS at both 5 and 10 years was 87% (95% CI: 72%–100%), versus 35% (16%–53%) at 5 years and 12% (0%–24%) at 10 years after the same patients' first-line treatment. These results, in patients many of whom had multiple previous relapses, contrast markedly with the declining RFS seen after sequential lines of treatment in patients receiving a purine analogue alone, as reviewed above.

Caution is needed in interpreting these results. It is possible that, in some patients, the BM may have been more heavily infiltrated at the start of first-line treatment than at the time of combination therapy. Also, 8/26 of our combination-treated patients had not previously received the particular purine analogue used in the combination and it is possible that switching to the alternative agent may in itself have led to an improved outcome, due to a lack of cross-resistance between pentostatin and cladribine [45]. Lack of cross-resistance is confirmed by another of our other patients (not in the rituximab-combination series) who was refractory to pentostatin but remains in remission 22 years after receiving cladribine as a single-agent. On the other hand, 9/26 combination-treated patients previously had only a partial response and/or a short remission (<2 years) after an earlier line of treatment using the same purine analogue as was given in the combination, showing clear evidence for the added benefit of the rituximab component.

Second malignancies

The rate of second malignancies observed in the published series varied from 0% at two years median follow-up [41] (Table 1) to 23% at 9 years median follow-up [31] (Supplementary Table S1). In our series 31/233 patients (13%) developed known second malignancies (28 *after* treatment for HCL), excluding non-melanoma skin cancers. This was equivalent to the age/sex-matched incidence of cancers in the general population (expected n = 33) [19]. Four of these malignancies were leukaemias/lymphomas and two were myeloproliferative disorders. In the Scripps Clinic study of younger patients with very long follow-up (median 21 years) no excess incidence of malignancies was seen [37]. On the other hand, Cornet et al. [39] reported an excess incidence, with a standardized incidence ratio of 1.86 (95% CI: 1.34–2.51), increasing to 5.32 (95% CI: 2.90–8.92) for second haematological malignancies. There was no significant difference between pentostatin and cladribine. Cornet et al. [39] reviewed the

literature concerning second malignancies in HCL, including HCL series as well as large epidemiological studies from population-based registries. They cited several reports of an increased risk, particularly of second haematological malignancies and concluded that the increased risk is more likely to be related to the disease itself than the treatment. Intrinsic immune alterations in HCL could provide a mechanism for additional malignancies through diminished anti-tumour defence [39].

Deaths and overall survival

There were 45 deaths in our series (19%), equivalent to the age/sex-matched general population rate (expected n = 57, not significant) [19]. Overall survival 15 years after first treatment was 78%. Only 8 deaths (3%) were directly related to HCL, following refractory disease [19]. Death rates in other series were similar. Zinzani et al. reported 15 deaths (12.5%); 5 deaths (4%) were due to refractory HCL [18]. In the Mexican series 10-year OS was 91% [42]. In the Scripps clinic series of younger patients there were 13 deaths (16%), with a standardized mortality (observed-to-expected) ratio of 1.85 (95% C.I. 1.07–3.18), representing a small increase in the risk of death (p = 0.04) [37]. Although the causes of death were various, 10/13 patients had a documented relapse of HCL before death. Kaplan–Meier curves show that OS 15 years after the first course of cladribine was better for complete responders (95%) than for partial responders (50%; log-rank p = 0.0008) [37].

In the Turkish series there were 8 deaths (8.5%) and survival 5 years after cladribine treatment was 96% [40]. However 4 of these patients had variant HCL and died due to progressive disease. The remaining 4 patients died due to sepsis before chemotherapy, aspergillus infection during therapy, development of acute myeloid leukaemia and acute myocardial infarction, respectively. Cornet et al. [39] reported 11 deaths (2%) directly related to HCL (disease evolution: n = 4; infectious complications secondary to treatment: n = 7), with similar OS 10-years after pentostatin (86%) and cladribine (93%). As these latter two series show, treatment-related mortality remains an issue, in spite of improvements in infection management and prophylactic care.

Prognostic factors

Several studies have examined whether there are factors which predict CR, relapse, RFS or OS after purine analogue treatment. In our earlier review [17] we showed several baseline clinical features which were identified as significant prognostic factors in individual series using either pentostatin or cladribine, but with little consensus [8,13,14,28,30–32]. These included anaemia, thrombocytopenia, adenopathy, splenomegaly, leukocytosis and older age. More recently, leukocytosis was found to predict a worse response in the Turkish study, though this may have been due to the inclusion of 5 patients (5%) with HCL-variant [40].

In our series, no variable was found to predict a CR [36] and, with very long-term follow-up, factors predicting OS become increasingly difficult to identify, as deaths in older age from other causes increasingly confound the analysis. The most significant predictor of longer RFS in multivariate analysis was attainment of a CR [19]. In addition, the median RFS for patients with low hemoglobin (<10 g/dL) and/or low platelets (<100 × 10^9/L) was 9 years versus 20 + years (not reached) for all others (p < 0.0001). A CR was the only factor significantly associated with longer second or subsequent RFS [19].

Baseline tissue samples for assessing the prognostic significance of molecular markers are not available from long-term series, but later studies have identified unmutated *IGHV* genes, *VH4–34* usage and *TP53* gene mutation as factors adversely affecting response to cladribine, often in association with a bulky spleen and leukocytosis [46,47].

There has been some discussion about whether the prognosis for patients in CR can be further refined by whether or not minimal residual disease (MRD) is present. Sigal et al. [16] identified 19 patients from the Scripps Clinic who were in continued CR at a median of 16 years from cladribine treatment, of whom 47% (9/19) were MRD-negative, 37% (7/19) MRD-positive and 16% with morphologic evidence of HCL. Thus patients with MRD and even gross morphologic disease can live many years without relapsing. Lopez et al. [38] found that the median time elapsing between first and second-line treatments was 97 (38–156) months in MRD-positive patients (n = 40) versus not reached

in MRD-negative patients (n = 42; p = 0.05). Reviewing the literature, they concluded that the persistence of MRD after therapy with purine analogues is predictive of eventual disease recurrence.

Treatment guidelines and patient management

First line purine analogue treatment

Informed by these results from the published series, the purine analogues, pentostatin and cladribine, are still the first-line treatments of choice today, as confirmed by recent guidelines [25–27].

The choice of purine analogue and treatment schedule

Pentostatin and cladribine have similar efficacy. First-line ORR, CR rates, relapse rates and RFS were not significantly different between the two agents in our own and other studies, though none of these studies provided a randomised comparison [19,38,39]. Thus the choice between pentostatin and cladribine as first-line treatment is a matter of availability, convenience and cost.

Treatment schedules for pentostatin and cladribine are available in the guidelines [25–27]. Pentostatin is given at 4 mg/m^2 every 2 weeks until maximum response, plus one or two extra injections. With cladribine, subcutaneous delivery may be the most convenient option and appears to have equal efficacy with the intravenous form [23,24]. We have switched from a 7-day continuous intravenous infusion of cladribine 0.1 mg/kg/day to subcutaneous cladribine at a dose of 0.14 mg/kg daily for 5 days [15]. This has advantages for patients in terms of convenience, safety (no intravenous line), and side effect profile (no infusion-related reactions), and for the healthcare system in terms of capacity and cost, without any evidence of a negative impact on outcome.

Supportive care

Infections and treatment-related mortality remain a threat and appropriate prophylaxis and infection management, as described in the guidelines, is imperative [25–27].

The importance of assessing response

There is compelling evidence from the published series that patients who only achieve a PR in response to purine analogue treatment: are more likely to relapse than those who achieve a CR (Table 1 & Supplementary Table S1) [4,12,15,31–33,37,40]; relapse earlier than patients in CR [31,32,35,37,40]; and hence have shorter RFS (Fig. 1) [15]. There is also evidence of shorter OS after a PR than after a CR in younger patients [37]. Further, it is likely that patients who fail to obtain a CR may have impaired quality of life, due to cycles of returning disease and retreatment.

The assessment of disease clearance from the BM after completing treatment is therefore an important endpoint of the initial treatment and should be the standard of care [15,25–27]. For this assessment a good-quality BM trephine biopsy with immunohistochemistry is the gold standard. However, evidence is emerging that alternatives more acceptable to patients, such as 8-colour flow cytometry using peripheral blood or a BM aspirate, may in future be used instead of a trephine biopsy without loss of accuracy [48]. With pentostatin this assessment should be performed after 8 to 10 cycles of treatment when the full blood count has returned to normal (though lymphopenia will persist) [25–27]. Following cladribine therapy there is often a delay in clearance of BM disease and assessment at 4–6 months after the end of treatment is recommended [25–27].

Converting a partial to a complete response

If the assessment shows evidence of remaining disease, further treatment to establish a CR is recommended [15,18,25,26]. Due care should be given to avoid toxicity and deeper immunosuppression. The addition of 6–8 doses of rituximab, delivered either concurrently or shortly after the purine analogue, may help to achieve this goal [25]. With pentostatin, if a CR has not been attained after 10–12 injections, further pentostatin alone may not be effective [19], in which case the addition of rituximab may be considered [25]. With cladribine, we give a repeated cycle 4–6 months after the first cycle [15] and one may consider adding rituximab to the second cycle of cladribine [25].

It can be difficult for the patient to contemplate further cladribine treatment after some months of recovering health. There is a need to discuss with the patient the relative merits of further immediate treatment to establish a CR, with the likelihood of a much extended remission, versus freedom from any further current intervention, but with the prospect of an earlier return of the disease and a poorer long-term outlook.

Long term patient management

With improved management, in our HCL series which now has over 300 patients, only 3 patients have died in the past 15 years of causes directly related to HCL. Thus, long-term survival is now truly long-term, with most patients having a normal life expectancy [19].

Follow-up

Patients should be followed closely during treatment and for several months after completion of therapy, with special attention to appropriate surveillance and treatment for infections resulting from myelosuppression [49].

For patients who fail to respond to purine analogue treatment, or who relapse within a few months, tests to confirm the diagnosis of HCL should be performed, to exclude other similar disorders such as HCL-variant [26].

Patients who remain in PR may require close monitoring, but for those in CR follow-up once or twice yearly may be sufficient after the first year, with a view to identifying any HCL-related health issues. There does not appear to be a plateau in this disease and relapses may occur even after 20 years [37].

Salvage treatment with chemo-immunotherapy

As with first-line therapy, the aim of salvage treatment is to achieve a CR, in order to secure a long-term second remission and minimise patients' vulnerability to yet further relapses. We have shown that a CR after a second-line or third-line purine analogue may be as durable as a first-line CR [19]. However, although single-agent purine analogues continue to be effective as salvage therapy, with each successive line of treatment the likelihood of achieving a CR diminishes [15,18,30,31,33,35,37,40] and RFS becomes shorter [15,18,39]. In contrast, the combination of a purine analogue with rituximab has proven efficacy as salvage treatment, with minimal toxicity and a high CR rate [20–22,43]. The guidelines therefore suggest this combination for patients who have relapsed [25,27]. The choice of purine analogue will depend on the duration of first remission: if short, i.e. <2 years, use the alternative agent; if longer (>2 years) retreat using the same agent [25,27].

In updating our own series, above, we have shown that this combination can lead to long remissions, even in multiply-relapsed patients. Due to the relapses seen in two of our patients who received only 4 doses, we recommend that 6–8 doses should be given.

Treating refractory disease

Another role for an anti-CD20 monoclonal antibody such as rituximab is to treat patients who are refractory to cladribine or pentostatin [25,27]. However, although the combination of rituximab with the alternative purine analogue may be effective in non-responders, data are currently lacking.

Newer agents are available for patients who do not respond to, or relapse after chemo-immunotherapy, such as the *BRAF* inhibitors vemurafenib and dabrafenib, the *MEK* inhibitor trametinib and recombinant immunotoxins such as moxetumomab pasudotox, which binds to CD22. These agents are explored in the chapters by Zenz and Kreitman in this issue.

Predicting outcomes after purine analogue therapy

In this rare disease, data are still sparse regarding prognostic factors and their implications for treatment. International collaborations led by the Hairy Cell Leukemia Foundation may begin to

provide answers to such questions. As yet there is no prognostic factor which will modify the choice of first-line treatment.

At relapse, the presence of aggressive disease, shown by failure to achieve a first-line CR, early relapse (<24 months), unmutated *IGHV* genes, *TP53* gene mutation, *VH4–34* use, BM failure, leukocytosis and bulky disease, may indicate the need to consider alternatives to chemo-immunotherapy, such as immunotoxins or *BRAF* and *MEK* inhibitors [26].

Failure to achieve a CR has been shown to predict a poorer long-term outcome in many of the series reported above. MRD positivity is also a predictor of shorter time to relapse in some patients [16,38], but there is insufficient evidence to suggest that patients in CR should be re-treated until MRD negativity is reached, except as part of a clinical trial [25].

Summary

The purine analogues pentostatin and cladribine remain the first-line treatment of choice in HCL, offering an excellent long-term outlook for patients. Both purine analogues are equally effective and the choice can be made on the basis of cost, convenience and patient or physician preference. Guidelines are available concerning treatment schedule, prophylaxis and the management of infections.

The attainment of a CR is important for long-term relapse-free survival. It is therefore essential that, after 8–10 courses of pentostatin, or 4–6 months after cladribine treatment, an assessment of response should be made, either by BM biopsy (the gold standard) or by flow cytometry. Patients still in PR may then be given further treatment with the same purine analogue, with or without rituximab. Studies are needed to determine the best treatment schedule to convert a PR to a CR.

At relapse, chemo-immunotherapy (pentostatin or cladribine with the addition of rituximab) shows documented evidence of efficacy, with a high CR rate and long remissions. Studies are needed to determine the optimum regimen for the rituximab component, but we recommend 6–8 doses, given either concurrently with the purine analogue or sequentially. For patients failing to respond to purine analogues, or for those relapsing again after chemo-immunotherapy, newer therapies are available.

The majority of patients with HCL can now expect a normal lifespan, due to the effectiveness of the purine analogues, improved management of infections and the ability to salvage patients with chemo-immunotherapy after relapse. The achievement of a CR is critical to this success and should be the goal of therapy at each stage.

Practice points

- With the aim of establishing long-term relapse-free survival, it is important to attain a complete response to treatment.
- An assessment of response by bone marrow biopsy, or equivalent, is therefore an integral part of the treatment schedule, following 8–10 courses of pentostatin, or 4–6 months after cladribine treatment.
- If a complete response has not been attained, further treatment with the same agent is recommended, unless contraindicated. Evidence in this setting is limited, but it may be beneficial to add 6–8 doses of rituximab.
- Though evidence is again limited, chemo-immunotherapy may also be used for non-responders to single-agent purine analogue therapy, switching to the alternative purine analogue.
- Combination chemo-immunotherapy (pentostatin or cladribine with the addition of rituximab) has proven efficacy as a salvage treatment.
- For non-responders, or those who relapse after chemo-immunotherapy, newer agents such as *BRAF* inhibitors or immunotoxins are available.

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Research agenda

- There have been few randomised trials in HCL. It is to be hoped that the collaborative research being initiated by the HCL Foundation and others will lead to more such trials.
- It is not known whether patients with poor prognosis would benefit from the addition of an anti-CD20 monoclonal antibody, such as rituximab, to their first-line purine analogue.
- Research is needed to establish how best to convert a partial response to a complete response after a standard course of first-line pentostatin or cladribine.
- The optimum regimen for the rituximab component of combination chemo-immunotherapy needs to be established: the number of doses, the frequency and whether rituximab should be given concurrently with the purine analogue or sequentially.

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Conflict of interest

CED is on an advisory board for Roche. ME and DC have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.beha.2015.09.004.

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