Current Management of Hairy Cell Leukemia

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Hairy cell leukemia (HCL) is a B-cell chronic lymphoproliferative disorder characterized by splenomegaly, pancytopenia, circulating lymphocytes displaying prominent cytoplasmic projections and reactive marrow fibrosis [1, 2]. HCL usually has an indolent disease course, and similarly to chronic lymphocytic leukemia , patients who are asymptomatic do not require therapy. However, treatment should be considered for symptomatic or cytopenic patients. Treatment is indicated for patients with significant neutropenia, thrombocytopenia, symptomatic splenomegaly, constitutional symptoms due to HCL or recurrent serious infections [3].

The first active agent for this disease was interferon-α (IFN-α) which can produce a complete response (CR) in approximately 10% of HCL patients and a partial response (PR) in the majority of remaining patients [4-7]. More recently, new purine nucleoside analogs (PNA), cladribine (2-chlorodeoxyadenosine, 2-CdA) and pentostatin (deoxycoformycin, DCF) have become a gold standard in the treatment of this disease [8-11].]. 2-CdA and DCF are the drugs of choice in the treatment of HCL. Both agents are equally active, and have impressive long-term effectiveness [5]. However, monoclonal antibody (MoAb) directed against CD209 and immunotoxins directed against CD22 or CD25 have been introduced and are currently a promising novel approach to the treatment of resistant HCL [12-14].

Cladribine

Multiple studies demonstrated that 2-CdA induces durable and unmaintained CR in about 80% of patients after a single course of therapy [15-23]. 2-CdA is administered either as a continuous i.v. infusion at a dose of 0.09 mg/kg over a 5-7 days period or as 2-hour i.v. infusion at a dose of 0.12 mg/kg for 5-7 days. However, similar results were achieved when the drug was given in subcutaneous injection [19,24].Patients in apparent clinical and hematological remission following a single course of 2-CdA administration may have residual disease detected with the use of flow cytometry or molecular assay .2-CdA is also highly effective in relapsed disease. Goodman et al. [20] has reported the results of re-treatment with this agent. The overall response rate of relapsed patients who were retreated with 2-CdA was 90% with 75% achieving a CR and 10 (17%) a PR. The median second response duration for all responders was 35 months while the median time to first relapse was 42 months. The second relapse was observed in 20 patients and 10 of them received second re-treatment with 2-CdA. Overall response rate was 80% including 60% CR. The median third response duration was 20 months.

2-CdA is also an effective drug when administered at a dose of 0.15 mg/kg in 2-hour infusion once a week over 6 course .[22]. In our randomized study we compared weekly administration of 2-CdA (0.12 mg/kg in 2-h i.v. infusion once a week for 6 weeks) with daily administration (0.12 mg/kg in 2-h i.v. infusion for 5 consecutive days) [23]. The final results of this study indicate that both CR and overall response (OR) rates were similar in compared groups. There was no statistically significant difference in toxicity between groups. Moreover, HCL treatment with weekly 2-CdA infusion is not safer than standard 5-day 2-CdA.

Pentostatin

DCF is also a highly active agent in HCL[25-27]. The drug was usually used at a dose of 2-4

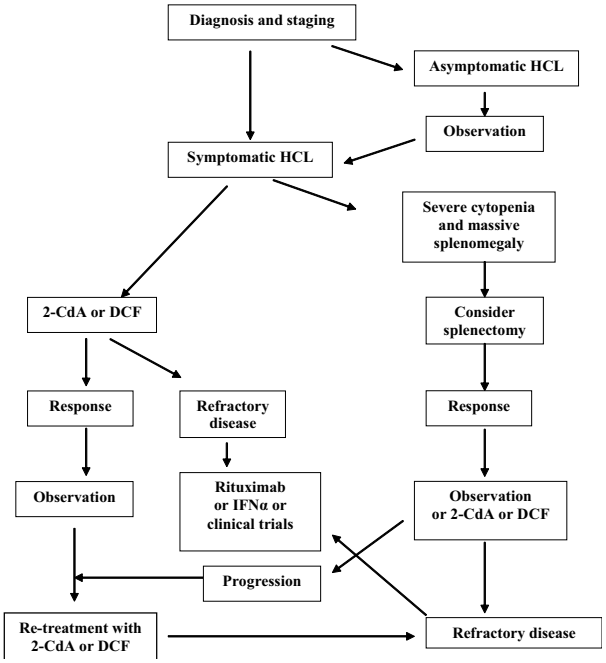

Fig 1. Proposed treatment algorithm for hairy cell leukemia (modified from [8]).

mg/m^2 i.v. every second week although other schemes were also applied. Ranges of CR varied from 40 to 90% regardless of prior treatment with IFN-α or splenectomy .The drug is well tolerated in HCL, especially when neutropenia is not severe or there is no history of life-threatening infections. Myelosuppression is the main toxicity and may require delays in planned chemotherapy schedule.

A randomized study comparing DCF with IFN-α has demonstrated that DCF produced a higher CR and PR rate with more durable responses in HCL [7]. In that study patients were randomized to receive either IFN-α (3x10^6/l subcutaneously 3 times per week) or DCF (4 mg/m^2 i.v. every 2 weeks). Patients who did not respond to initial treatment were crossed over. Among IFN-α patients, 17 of 159 (11%) achieved a confirmed CR or PR. Among DCF patients, 117 of 154 (76%) achieved a confirmed CR and 121 of 154 (78%) had a confirmed CR or PR. Response rates were significantly higher ($p < 0.0001$) and relapse free survival was significantly longer with DCF than IFN-α ($p < 0.0001$).

Subsequently, long-term data on duration of overall survival and relapse-free survival data from this study were reported [27]. Estimated 5- and 10-year survival rates for all patients were 90% and 81% , respectively. Moreover, only 2 of 40 death were attributed to HCL. Other long-term observations also confirmed that DCF induces a high rate of long-lasting CR both in patients previously untreated and in patients pretreated with IFN-α or splenectomy [26,29].

2-CdA and DCF seem to induce similar high response rates but only a large randomized trial with the two agents will be able to evaluate the CR rates, duration of response, recurrence rates and adverse events, that have appeared to be comparable so far.

Recently, Else et al. [29] have reviewed a series of 219 patients with HCL, with median follow-up from the diagnosis of 12.5 years (range 1.0- 34.6 yrs) treated either with DCF (n= 185) or 2-CdA (n= 34), to compare the effectiveness of these agents. Overall response to DCF was 96% with a CR in 81% and median disease free survival (DFS) of 15 years. Response to first line 2-CdA was 100% with a CR in 82% and DFS of 11+ years. DFS showed no plateau in both groups. The relapse rates at 5 years and 10 years were 24% and 42%, respectively, with DCF and 33% and 48% with 2-CdA. Survival at 10 years was 96% in DCF group and 100% in 2-CdA group. This study has confirmed previous observations that DCF and 2-CdA are equivalent in the treatment of HCL. However, 2-CdA affords the convenience of a single course of administration. Patients treated with PNA do relapse and the overall survival curves have not reached a plateau, which indicates that cure has not been secured.

Rituximab and immunotoxins

HCL presents the highest percentage of CD20 expression of lymphoproliferative disorders. Recently, rituximab as well as anti-CD22 and anti-CD25 immunotoxins have been investigated in refractory and/or relapsed HCL [5,30]. The use of MoAb therapy for the treatment of HCL offers also great promise and potential for improving progression free survival [42-57].

Lauria et al. [12] treated patients with HCL, who had progressed after prior therapy with 2-CdA and/or DCF, with rituximab. All patients received 375 mg/m^2 i.v. of rituximab once a week at 4 dose. Overall, out of 10 treated patients one achieved a CR, 4 - a PR and 3 - a minor response..

Twenty-four HCL patients reported recently by Nieva et al. [31] were treated with standard doses of rituximab. All of them relapsed after prior treatment with 2-CdA. Six patients achieved a response following rituximab including 3 (13%) with a CR and 3 (13%) with a PR. At a median follow-up of

14.6 months, 2 responders relapsed. Even better result were presented by Thomas et al. [32]. Fifteen patients with relapsed or primary refractory HCL after 2-CdA or DCF received rituximab 375 mg/m^2 weekly at a total of 8 planned doses. The overall response rate was 80% including 53% CR.

Rituximab seems to be an ideal drug for elimination of MRD in HCL patients after treatment with PNA . Cervetti et al. [33] evaluated a role of this antibody in 10 patients previously treated with 2-CdA. Before starting rituximab, two patients were in CR, six in PR and two showed no significant response to 2-CdA. Rituximab was infused once a week at a dose of 375 mg/m^2 for four doses. Two months after the end of rituximab therapy, all evaluated patients were in hematological CR. Moreover rituximab increased percentage of molecular remission up to 100% one year after the end of treatment. These results have been recently confirmed by Ravandi et al. [14]. They have treated 13 patients, 11 with newly diagnosed disease and two after failure of one prior therapy with 2-CdA at a dose of 5.6 mg/m^2 daily for 5 days followed by rituximab at a dose of 375 mg/m^2 weekly for 8 weeks. All patients achieved a CR, and MRD was eradicated in 12 (92%) of the patients.

Promising results in patients with resistance to purine analogues have been obtained with two immunotoxins BL22 and LMB-2 targeting CD22 and CD25, respectively [13,34,35]. Recently, Kreitman et al. [13] have reported the results of their study testing the safety and efficacy of recombinant immunotoxin containing anti-CD22 variable domain (Fv) fused to truncated Pseudomonas exotoxin (RF B4 (dsFv)-PE-38) named BL22 . Sixteen HCL patients who were resistant to 2-CdA were included into the study. All patients had circulating hairy cells that expressed CD22. BL22 at doses between 0.2-4.0 mg was administered as a 30 min intravenous infusion every other day to a total of 3 doses. Of 16 patients treated with BL22, 11 (69%) had a CR and 2 had a PR. Common toxic effect was transient hypoalbumina and the elevated aminotransferase level. Two patients developed reversible hemolytic uremic syndrome.

Current indications for splenectomy and interferon-α

With the introduction of PNA, the indication for splenectomy is extremely limited. The removal of the spleen may be appropriate in patients with resistant massive symptomatic splenomegaly or results in severe cytopenia following PNA therapy [60], and when progressive HCL developed during pregnancy [36,37]. Splenectomy may be also required for diagnostic reasons in patients with primary splenic HCL and in rare patients refractory to PNA, IFN-α and MoAb . Splenic rupture is also rare indication for splenectomy [58].

IFN-α may still have a place in HCL in pregnancy [64] and in the patients presenting with very severe neutropenia to increase neutrophil count prior to PNA therapy [38,39]. There is no significant role for IFN-α in improving the proportion and the duration of CR in HCL patients previously treated with DCF. In the study performed by Marotta et al [40] 135 patients who obtained CR or PR after treatment with DCF were randomized to receive IFN-α or not. Progression of disease was observed in 8 and 12 patients, with a median time of 27.8 and 26.9 months, respectively.

Conclusions

Treatment of progressive symptomatic HCL includes a variety of pharmacological approaches such as INF-α, DCF and 2-CdA, which have significantly improved the disease prognosis. 2-CdA and DCF seem to induce a similar high response rate and a long overall survival. They are also active in relapsed patients. About 80% of patients treated with 2-CdA or DCF survive for at least 10 years. In patients, who failed PNA therapy, anti-CD20 MoAb rituximab and anti-CD22 (BL22) immunotoxin appear extremely effective. Future studies should be directed to optimizing the therapy for minimal residual disease as well as whether the introduction of new effective agents will translate into cure. A proposed flow-chart for therapeutic decision-making in the treatment of HCL is outlined in Fig 1.

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