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Research paper

Primary peg-filgrastim prophylaxis versus filgrastim given "on demand" for neutropenia during therapy with cladribine for hairy cell leukemia

Tamar Tadmor[a,b,*], Ilana Levy[c], Yair Herishanu[d], Neta Goldschmidt[e], Osnat Bairey[f], Mona Yuklea[g], Lev Shvidel[h], Riva Fineman[i], Ariel Aviv[j], Rosa Ruchlemer[k], Andrei Braester[l], Najib Dally[m], Ory Rouvio[n], Adir Shaulov[e], Uri Greenbaum[n], Michal Inbar[b], Aaron Polliack[e]

[a] Hematology Unit, Bnai-Zion Medical Center, Haifa, Israel
[b] The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel
[c] Internal Medicine B, Bnai Zion Medical Center, Haifa, Israel
[d] Department of Hematology, Tel-Aviv Sourasky Medical Center and Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel
[e] Department of Hematology, Hadassah Hebrew University Medical center, Jerusalem, Israel
[f] Department of Hematology, Rabin Medical Center and Sackler School of Medicine, Tel-Aviv University, Tel Aviv Petah-Tikvah, Israel
[g] Department of Hematology, Meir Medical Center, Kfar-Saba, Israel
[h] Hematology Unit, Kaplan Medical Center, Rehovot, Israel
[i] Department of Hematology & Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel
[j] Hematology Unit, HaEmek Medical Center, Afula, Israel
[k] Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel
[l] Hematology Unit, Galilee Medical Center, Nahariya, Israel
[m] Hematology Unit, Ziv Medical center, Safed, Israel
[n] Department of Hematology, Soroka University Medical Center, Beer-Sheva, Israel

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ABSTRACT

Background: Major advances in the treatment of patients with hairy cell leukemia (HCL) have been made following the introduction of purine analogues. The major significant short-term toxicity of cladribine therapy are neutropenia and neutropenic fever (NF) which may be life-threatening.
Aim: In this retrospective study, we compared the incidence and duration of neutropenia and hospitalization in patients with HCL treated with cladribine followed by peg-filgrastim as primary prophylaxis versus daily filgrastim given "on demand" according to absolute neutrophil count (ANC).
Methods: Medical records of patients with HCL diagnosed and followed in 12 medical centers in Israel during 1985–2015 were examined for details of disease at diagnosis. The efficacy of peg-filgrastim and filgrastim was assessed by evaluating the incidence of neutropenia (ANC $< 1.0 \times 10$ [9]/L), number and length of hospitalizations, and number of days from the last day of therapy to recovery of ANC to $> 1.0 \times 10$ [9]/L.
Results: The study population included 202 patients with HCL, 159 of whom (80.7%) were treated with cladribine; 78 patients (49%) required hospitalization for the administration of broad-spectrum antibiotics due to NF. Twenty-eight (19%) patients were treated with peg-filgrastim as primary prophylaxis, while 74 (64%) received filgrastim "on demand" due to neutropenia. Median length of hospitalization, and nadir duration were 8 and 18 days respectively ($p = 0.71$, $p = 0.44$).
Conclusions: Infectious complications post-cladribine treatment remain high. No difference was found in terms of incidence of NF, number of febrile days, and nadir duration in patients receiving primary peg-filgrastim prophylaxis compared to filgrastim given on demand. Both approaches are justifiable, and the choice remains at the physician's discretion.

1. Introduction

Hairy cell leukemia (HCL) is a rare B-cell lymphoproliferative disorder which accounts for 2% of leukemias. This disorder is characterized by pancytopenia, splenomegaly and bone marrow infiltration by typical mononuclear cells displaying cytoplasmic projections

* Corresponding author at: Hematology Unit, Bnai-Zion Medical Center, 47 Golomb Street, Haifa, 31048, Israel.
E-mail address: tamar.tadmor@b-zion.org.il (T. Tadmor).

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resembling fine hair. [1] Cladribine (2-CdA), a purine nucleoside analog, is the widely accepted treatment for HCL since its introduction in the 1980s. [2] Therapy with this agent is effective, and a single course of treatment successfully induces complete and long-lasting remissions in most patients,[3] but it is also immunosuppressive. After administration of 2-CdA, as many as 71% of patients develop grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5 × 10^9/L), and 42% develop neutropenic fever (NF), which frequently requires hospitalization and administration of broad-spectrum antibiotics to prevent life-threatening infections. [2] Recombinant granulocyte-colony stimulating factor (G-CSF) products have been found to reduce NF incidence, hospitalization duration and the risk of infections. Thus, according to current guidelines [4], G-CSF is routinely administered to patients receiving regimens with an approximate risk of over 20% for NF [5]. Despite the fact that 2-CdA has been shown to cause a higher percentage of NF, there is no current recommendation for the routine use of G-CSF products in HCL treatment and this topic has not received wide attention until now. An earlier study reported in 1999 that patients with HCL receiving G-CSF (filgrastim) indeed experienced shorter neutropenic periods after 2-CdA treatment, but the incidence of NF was not significantly reduced. [6] Similarly, both the frequency and duration of hospitalization due to NF were not affected by filgrastim. Current HCL guidelines do not recommend routine administration of G-CSF. [1,7–9] Nevertheless, it is important to emphasize that despite this, in common practice hospitalized neutropenic patients do in fact receive filgrastim on demand, according to the level of their ANC.

Recently, a pegylated form of G-CSF (peg-filgrastim) with a longer half-life has been introduced in primary prophylaxis of NF. [10] It is administered as a single subcutaneous injection, which leads to lower costs and better compliance than filgrastim. Only one preliminary small-cohort study compared the efficacy of peg-filgrastim prophylaxis with therapy using filgrastim "on-demand" in reducing NF incidence in HCL patients. [11] Both products had similar effect; however, there appeared to be a trend (not statistically significant) toward shorter hospitalization and shorter neutropenic periods with peg-filgrastim.

The aim of this retrospective study is to compare the efficacy of the two G-CSF products in a large series of HCL patients treated in most of the medical centers in Israel.

2. Materials and methods

Data obtained from 202 patients with HCL treated in 12 medical centers in Israel during 1985–2015 was collected retrospectively. Diagnosis was based on histopathology reports and flow cytometric analysis of peripheral blood, bone marrow and/or spleen specimens and was established according to World Health Organization criteria. [1,3,10] We recorded details of the treatment given and analyzed outcomes after first-line therapy with cladribine given subcutaneously or intravenously.

The current cohort included 159 patients with HCL who received cladribine as first line therapy. We summarized clinical, demographic and biologic features. [12] We then collected data regarding the use of G-CSF as given based on each medical center's own approach, or as primary prophylaxis using peg-filgrastim given 24 h after the last day of cladribine therapy. In addition, data regarding number and time spent in hospital, duration of neutropenia defined as nadir duration (number of days from the last day of therapy until recovery of ANC to > 1.0 × 10^9/L), overall survival (OS) and progression-free survival (PFS).

Data were only collected after approval by the local institutional review boards of each medical center participating in the study and in accordance with the principles of the declaration of Helsinki.

2.1. Statistical analysis

Descriptive statistics were calculated for each of the variables. Data were expressed as mean ± standard deviation (SD) for normally distributed data, median and minimum-maximum range for non-normally distributed data, or as percentage frequencies. For survival analysis, univariate Kaplan–Meier analysis was performed. The day of diagnosis of HCL was used as the starting date for analysis. OS and PFS were calculated from the day of diagnosis until the date of last follow-up, death or relapse, respectively. Differences among variables were evaluated by the Pearson Chi-square test. Statistical significance was defined as p-value < 0.05.

3. Results

3.1. Baseline characteristics

Median age at diagnosis was 52 years [23–87], and 53 years age at initiation of therapy; 83% of treated patients were men. In terms of ethnicity, 85% were Jewish and 15% were Arab, Druze or other. 129 patients (81%) presented with enlarged spleen (diameter > 13 cm), with a median size of 15.9 cm [5–35 cm]. Median time from diagnosis to first treatment was 10.1 months [0–408]. Mean and median follow-up of the entire cohort were 7.5 and 5.2 years (0.1–40), and 5- and 10-years survival was 96% and 90.6% respectively. The median number of days of cladribine therapy was 5 [1–9] and the median and mean relative cumulative dose given was 50 mg, and 52.5 mg [27–80] respectively. Cladribine was administrated intravenously to 92 patients and subcutaneously to 56 patients (data missing in 11 patients). OS and time to next treatment were not significantly different for the two schedules. Mean and median survival post-therapy with cladribine was 4.6 and 5.6 years [0–19.24] respectively. Median white blood cells (WBC) count at first day of therapy was 2.8 × 10^9/L [0.5–45.4] and median ANC was 0.9 × 10^9/L [0.1–6.0]. 55% of patients started therapy with ANC < 1.0 × 10^9/L. Median hemoglobin on first day of therapy was 11.4 g/dL [5.3–16.5] and 43% of patients started therapy with hemoglobin < 11.0 g/dL. 84% patients started therapy with platelet count < 100 × 10^9/L and median count was 64.0 × 10^9/L [3.6–281].

3.2. G-CSF administration

Decision regarding the type of G-CSF to use was based entirely on the choice of the treating physician. Twenty-eight (19%) patients received primary peg-filgrastim prophylaxis given as a fixed dose of 6 mg, 24 h after the last injection of cladribine, as recommended. Data on G-CSF administration was missing in 15 patients. Of the 116 patients not receiving G-CSF prophylaxis, 42 (36%) did not require G-CSF as they did not develop NF, while 74 (64%) received filgrastim "on demand" later on because of neutropenic complications (infection, NF) (Fig. 1). It should be noted that HCL patients were followed for the development of neutropenia or its complications, generally at the discretion of the treating hematologist on a monthly basis.

When comparing patients who received peg-filgrastim primary prophylaxis (n = 28) with those who did not (n = 116), baseline clinical characteristics were similar, as were the rates of hospitalization and infection (Table 1). The only data that differed between the two groups was WBC at nadir (1.1 ± 1.3 × 10^9/L in the peg-filgrastim primary prophylaxis group vs. 0.9 ± 0.7 × 10^9/L in patients who did not receive primary prophylaxis, p < 0.001); no differences were seen in relation to ANC at nadir.

Among patients who did not receive peg-filgrastim prophylaxis (n = 116), we compared patients given filgrastim "on demand" (n = 75) with those who did not receive G-CSF at all (n = 41) (Table 2). Subcutaneous cladribine was less frequently given in patients who required filgrastim treatment later on (25%) than in those who did not require G-CSF (41%) (p = 0.008). Baseline hemoglobin (p = 0.005) and platelet counts (p = 0.008) were both lower in the filgrastim group, as were WBC and ANC at nadir (p < 0.001). The rate of infection was higher in the filgrastim group.

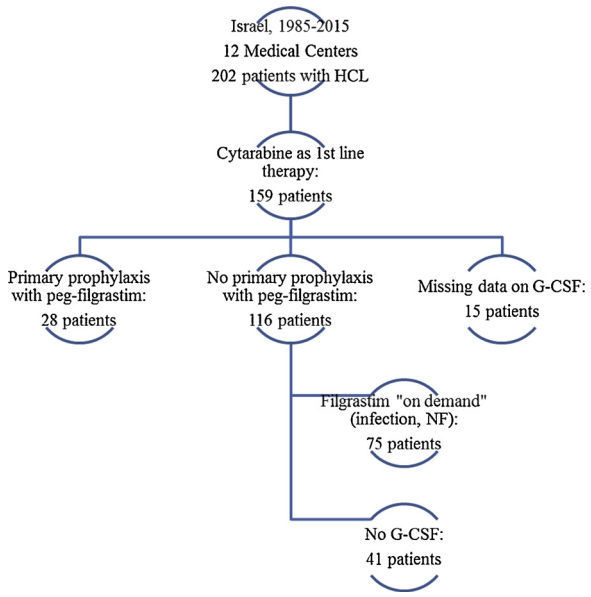

Fig. 1. Flow chart of patient's cohort.

Table 1
Baseline characteristics.

Characteristics	Peg-filgrastim primary prophylaxis (N = 28)	No primary prophylaxis (N = 116)	p
Age at diagnosis (years)	52.9 ± 10.9	54.1 ± 13.2	0.06
Gender: Male	23 (82%)	96 (83%)	0.86
Ethnicity:			
Jewish	14 (50%)	50 (38%)	0.58
Arab, Druze, Other	14 (50%)	66 (57%)	
Total cladribine dose (mg)	51.7 ± 10.2	52.9 ± 8.5	0.76
Cladribine route:			
Intravenous	14 (50%)	73 (63%)	
Subcutaneous	13 (50%)	35 (30%)	0.06
Unknown	1 (4%)	8 (7%)	
Spleen diameter (cm)	17.5 ± 5.7	16.2 ± 4.0	0.06
CBC at start of therapy:			
WBC (10^9/L)	4.0 ± 4.7	4.4 ± 5.4	0.96
ANC (10^9/L)	0.82 ± 0.75	1.2 ± 0.91	0.16
Hemoglobin (g/dL)	11.1 ± 1.9	11.4 ± 2.2	0.45
Platelets (10^9/L)	73.4 ± 52.9	69.1 ± 30.9	0.04
CBC at nadir:			
WBC (10^9/L)	1.1 ± 1.3	0.9 ± 0.7	< 001
ANC (10^9/L)	0.4 ± 0.4	0.4 ± 0.4	0.48
Neutropenic fever	19 (68%)	59 (51%)	0.11
Hospitalization	19 (68%)	56 (48%)	0.058

OS and PFS were not affected by G-CSF therapy (Fig. 2) nor by the rate of infection.

3.3. Hospitalization

78 patients (49%) required hospitalization for the administration of broad-spectrum antibiotics due to NF. Nineteen patients (68%) who had received peg-filgrastim prophylaxis were hospitalized due to NF, compared to 56 patients (48%) who did not receive prophylaxis (p = 0.058).

3.4. Death

Overall, eight (5%) patients died during follow-up. We examined the clinical and laboratory characteristics of the three patients who died within the first year after treatment and could not identify any high-risk feature other than age and sex. Their median age was 76 years [63–87] and all three were men who needed hospitalization after treatment; two of them due to infection. None of the patients died due to infectious complications.

Table 2
Comparison of baseline characteristics of patients that did not receive peg-filgrastim primary prophylaxis.

Characteristics	Filgrastim "on demand" (N = 75)	No G-CSF (N = 41)	p
Age at diagnosis (years)	51.6 ± 12.5	55.7 ± 13.1	0.07
Gender: Male	59 (79%)	38 (93%)	0.24
Total cladribine dose (mg)	53.6 ± 9.1	51.7 ± 7.1	0.20
Cladribine route:			
Intravenous	53 (71%)	18 (44%)	0.05
Subcutaneous	19 (25%)	17 (41%)	0.008
Unknown	3 (4%)	6 (11%)	0.12
Spleen diameter (cm)	16.7 ± 4.9	15.9 ± 3.2	0.29
CBC at start of therapy:			
WBC (10^9/L)	4.8 ± 6.5	4.4 ± 3.7	0.68
ANC (10^9/L)	1.1 ± 1.0	1.2 ± 0.6	0.51
Hemoglobin (g/dL)	10.9 ± 2.1	12.0 ± 2.3	0.005
Platelets (10^9/L)	62.0 ± 29.3	76.0 ± 29.3	0.008
CBC at nadir:			
WBC (10^9/L)	0.71 ± 0.43	1.1 ± 0.57	< 001
ANC (10^9/L)	0.3 ± 0.23	0.56 ± 0.38	< 001
Nadir duration (days)	25 ± 27.2	18.7 ± 17.9	0.13
Infection	45 (60%)	12 (29%)	< 001
Relapse	15 (20%)	14 (34%)	0.23
Death	4 (5%)	2 (5%)	1.0

Legend: ANC: Absolute Neutrophil Count; CBC: Complete Blood Count; G-CSF: Granulocyte-Colony Stimulating Factor; WBC: White Blood Cells.

3.5. Discussion

Hairy cell leukemia is a rare disease with unique biological features and a favorable outcome with excellent long-term survival after treatment with purine analogues. [1,2] Characteristically frontline therapy with only one course of cladribine achieves an excellent response rate and prolonged progression free survival.2]

The main complications of the disease itself and of treatment are pancytopenia and neutropenia, which predispose patients to infections, particularly after initiation of therapy with purine analogues. [2,13]

In our study, pancytopenia and especially neutropenia were features in patients treated with cladribine and 49% of the patients required hospitalization due to NF.

Indeed, infectious complications are important and well recognized issues in these patients. [14] The above complications are due to both neutropenia and other inherent immune defects evident in patients with HCL which are related to decreased numbers of monocytes, dendritic cells and natural killer cells [15]. The most frequent infections encountered are pneumonia and bacteremia [15]. The incidence of infection or NF in patients who received first-line cladribine is reported to be between 32–40% [14] and this high rate could perhaps be reduced by changing the cladribine regimen used.

In this respect it is of interest that in 1999, Lauria et al. reported results of weekly administration of cladribine for a period of 6 weeks in a cohort of 30 patients with HCL. Efficacy in terms of complete remission and overall response rate was similar to that obtained after daily schedule of cladribine administration. Only 5/30 patients (16%) developed severe neutropenia and only 7% (2 patients) had NF. [16] These are much lower rates than generally reported, including those our study reports here. However, despite the obvious advantages of a weekly schedule, this was not adopted in most other centers, probably because the cohort was small. This weekly regimen will still require validation before it can be utilized as a possible approach to reducing

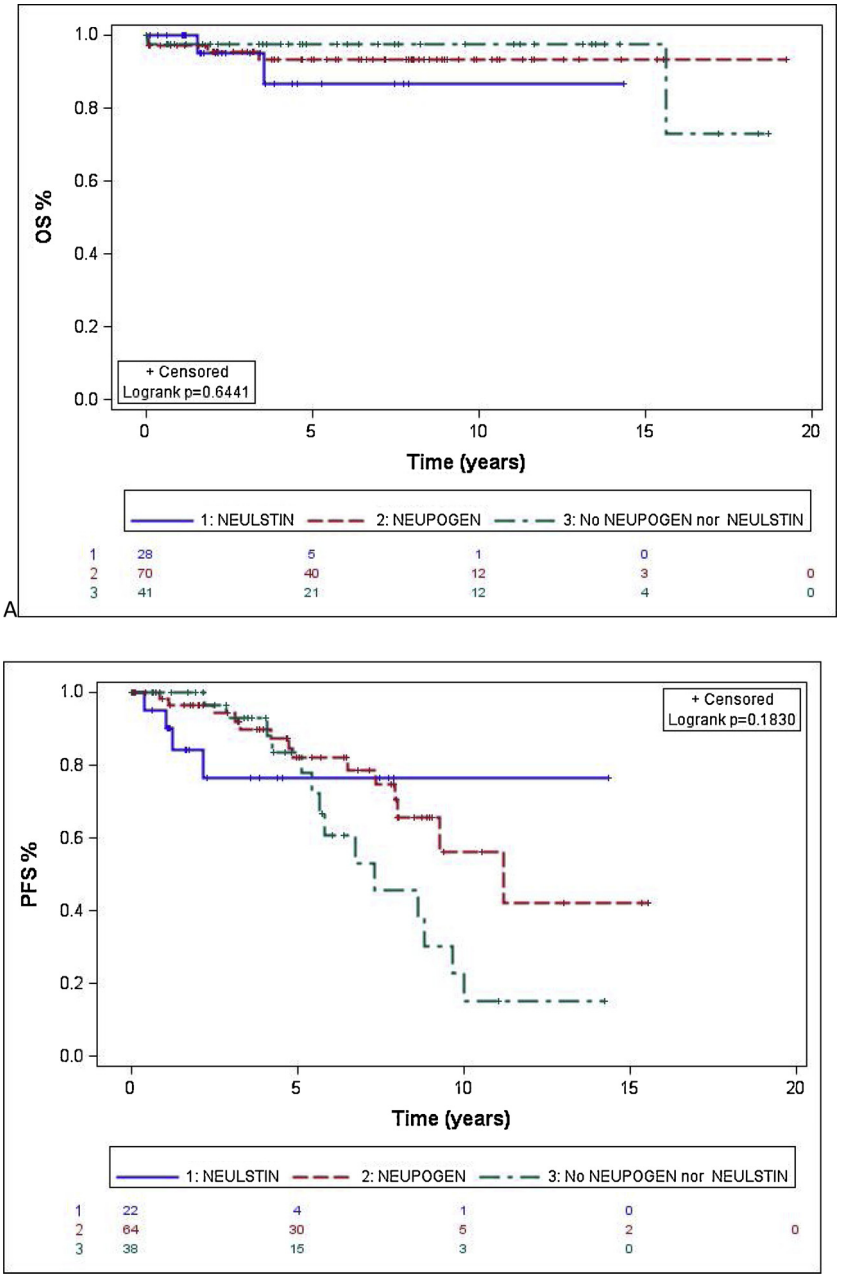

Fig. 2. Overall survival and progression-free survival based on the use of G-CSF.
Neulastin: Prophylactic peg-filgrastim (blue); Neupogen: Filgrastim "on demand" (red) or no G-CSF administration (green).

neutropenic complications in HCL.

One of the proposed mechanisms for the prominent pancytopenia and bone marrow "insufficiency" seen in HCL relates to a possible inadequate amount of colony stimulating factors within the bone marrow niche including G-CSF and IL-6. [13] Indirect evidence of growth factor deficiency has also been provided by *in vitro* studies. [17] In these older studies it was suggested that there was a deficiency of G-CSF production in HCL and that the use of this growth factor could abrogate this finding. Following the above hypothesis, it was speculated that monotherapy with G-CSF could also have anti−HCL activity but this beneficial effect was not observed once the growth factor was stopped after 4 months [17], showing that growth factor itself had no disease-modifying activity in vivo [18].

Several reports have recorded clinical experience regarding the prophylactic use of G-CSF aiming to prevent NF in HCL, most of which were individual case reports, some of them even from the pre-purine analog era. These include the experience with the combination of interferon alpha 2b and G-CSF which appeared to be active in patients with HCL,with increases of ANC within 2 weeks of administration. [19]

In 1995, Juliusson et al. evaluated the role of GM-CSF in patients with HCL treated with cladribine demonstrating that GM-CSF significantly reduced cladribine-induced lymphopenia but not the incidence of NF. [20] Data from a phase II study by Saven and co-workers compared patients treated with cladribine and G-CSF with a group of historical controls who did not receive this agent: G-CSF use reduced the number of days patients had neutropenia but did not reduce the number of febrile days nor influence antibiotic use. Based on this single study, guidelines for HCL do not recommend the routine use of G-CSF in HCL, but only in the event of severe neutropenia or NF. [8,9,21,22]

A slightly more active approach was recommended by the MD Anderson group for elderly patients, following American Society of Clinical Oncology (ASCO) guidelines [23] considering primary

prophylaxis with growth factors for this category of patients [24].

The use of the newer formula of G-CSF, peg-filgrastim, has been shown to be as safe and effective as daily injections of filgrastim, but with better patient compliance in several hematological and oncological disorders. [10,23]

However, data regarding its use in HCL is limited. In an earlier study, in a small cohort of patients we evaluated its use compared to G-CSF given on demand. [11] In that study we reported a trend towards a shorter duration of neutropenia and fewer days of hospitalization in the group of 9 patients treated with pegylated G-CSF. These early observations were not confirmed in the larger study we report here, where no differences in outcome were noted between cladribine-treated HCL patients receiving prophylactic peg-filgrastim and those treated with filgrastim "on demand".

It is worth noting that newer therapies are now being evaluated in patients with HCL and severe infections, such as the BRAF inhibitor vemurafenib [25]. It was used in three cases of HCL complicated with pancytopenia and severe infection and achieved rapid hematologic and clinical improvement, and deserves further evaluation in larger studies [25].

There are of course both strengths as well as limitations to our study. It is a multicenter study collecting both clinical and laboratory data from the vast majority of treated HCL patients in Israel over a 20-year period, with meaningful follow-up and findings. On the other hand it is a retrospective collection of data obtained from heterogeneous clinical approaches to G-CSF therapy in the different Israeli centers which probably did introduce selection bias. In addition, data and details regarding the type of infections are missing. Thus, prospective studies are indeed needed in order to compare the outcomes after prophylactic peg-filgrastim use versus filgrastim "on demand" in patients with HCL treated with cladribine.

3.6. Conclusion

In conclusion, infectious complications remain a relevant issue for patients with HCL treated with cladribine. Primary peg-filgrastim prophylaxis does not appear to influence the rate of NF, number of febrile days, or nadir duration when compared to filgrastim given "on demand". Further prospective studies are required in the future to compare these outcomes and to carefully assess the need for new guidelines relating to G-CSF therapy in HCL in the era of purine analogues.

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Conflict of interest

The authors have no conflicts of interest to declare.

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References

[1] M.R. Grever, O. Abdel-wahab, L.A. Andritsos, et al., Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia, Blood 129 (5) (2017) 553–560.
[2] A. Saven, C. Burian, J.A. Koziol, L.D. Piro, Long-term follow-up of patients with hairy cell leukemia after cladribine treatment, Blood 92 (6) (1998) 1918–1926.
[3] I. Levy, T. Tadmor, Time to cure hairy cell leukemia, Turk. J. Haematol. 34 (4) (2017) 289–290, https://doi.org/10.4274/tjh.2017.0296.
[4] G.H. Lyman, N.M. Kuderer, L. Balducci, Cost-benefit analysis of granulocyte colony-stimulating factor in the management of elderly cancer patients, Curr. Opin. Hematol. 9 (3) (2002) 207–214.
[5] M.S. Aapro, J. Bohlius, D.A. Cameron, et al., update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours, Eur. J. Cancer 47 (1) (2010) 8–32 2011.
[6] A. Saven, C. Burian, J. Adusumalli, J.A. Koziol, Filgrastim for cladribine-induced neutropenic fever in patients with Hairy Cell Leukemia, Blood 93 (8) (1999) 2471–2477.
[7] T. Robak, E. Matutes, D. Catovsky, P.L. Zinzani, C. Buske, Hairy cell leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 26 (Suppl. 5) (2015) v100–v107.
[8] W.G. Wierda, J.C. Byrd, J.S. Abramson, et al., Hairy cell Leukemia, Version 2.2018: clinical practice guidelines in oncology, JNCCN J Natl Compr Cancer Netw 15 (11) (2017) 1414–1427.
[9] E. Cornet, A. Delmer, P. Feugier, et al., Recommendations of the SFH (French Society of Haematology) for the diagnosis, treatment and follow-up of hairy cell leukaemia, Ann. Hematol. 93 (12) (2014) 1977–1983.
[10] G. Molineux, The design and development of pegfilgrastim (PEG-rmetHuG-CSF, Neulasta), Curr. Pharm. Des. 10 (11) (2004) 1235–1244.
[11] N. Goldschmidt, C. Ganzel, D. Attias, M. Gatt, A. Polliack, T. Tadmor, Pegfilgrastim prophylaxis for cladribine-induced neutropenia in patients with hairy-cell leukemia, Acta Haematol. 132 (1) (2014) 118–121.
[12] M. Inbar, Y. Herishanu, N. Goldschmidt, et al., Hairy cell leukemia: retrospective analysis of demographic data and outcome of 203 patients from 12 medical centers in Israel, Anticancer Res. 38 (11) (2018) 6423–6429.
[13] J. Schwarzmeier, C. Gasche, M. Hilgarth, W. Reinish, S. Gobl, R. Berger, Myelosuppression in Hairy cell leukemia: role of hairy cells, T cells and haematopoietic growth factors, Eur. J. Haematol. 52 (5) (1994) 257–262.
[14] E. Kraut, Infectious complications in hairy cell leukemia, Leuk. Lymphoma 52 (SUPPL. 2) (2011) 50–52.
[15] C.A. Dasanu, T. Ichim, D.T. Alexandrescu, Inherent and iatrogenic immune defects in hairy cell leukemia: revisited, Expert Opin. Drug Saf. 9 (1) (2010) 55–64.
[16] F. Lauria, M. Bocchia, G. Marotta, D. Raspadori, P.L. Zinzani, D. Rondelli, Weekly administration of 2-chlorodeoxyadenosine in patients with hairy-cell leukemia is effective and reduces infectious complications, Haematologica 84 (1999) 22–25.
[17] P. Resnitzky, Y. Barak, Y. Karov, A. Berrebi, R. Sharon, Hairy cell leukemia: defective production of granulocyte-macrophage colony-stimulating factor by peripheral blood cells, Isr. J. Med. Sci. 18 (8) (1982) 845–848.
[18] C. Christopoulos, A. Fortis, D. Nikzas, E. Anevlavis, The place of myeloid growth factors in the treatment of hairy-cell leukaemia, Clin. Lab. Haematol. 19 (2) (1997) 149–150.
[19] J. Osterholz, M. Wohlleber, C. Kahnt, K. Schumacher, The use of interferon-alpha and granulocyte colony-stimulating factor in hairy cell leukaemia with aplastic marrow, Eur. J. Haematol. 55 (2) (1995) 140–142.
[20] G. Juliusson, R. Lenkei, G. Tjonnfjord, D. Heldal, J. Liliemark, Neutropenic fever following cladribine therapy for symptomatic hairy cell leukemia: predictive factors and effects of granulocyte-macrophage colony-stimulating factor, Ann. Oncol. 6 (4) (1995) 371–375.
[21] M.R. Grever, BRAF inhibitor: targeted therapy in hairy cell leukemia, Blood 127 (23) (2016) 2784–2785.
[22] G. Jones, N. Parry-Jones, B. Wilkins, M. Else, D. Catovsky, Revised guidelines for the diagnosis and management of hairy cell leukaemia and hairy cell leukaemia variant*, Br. J. Haematol. 156 (2) (2012) 186–195.
[23] T.J. Smith, K. Bohlke, G.H. Lyman, et al., Recommendations for the use of WBC growth factors: American society of clinical oncology clinical practice guideline update, J. Clin. Oncol. 33 (28) (2015) 3199–3212.
[24] P.A. Thompson, F. Ravandi, How I manage patients with hairy cell leukaemia, Br. J. Haematol. 177 (4) (2017) 543–556.
[25] D.P. Shenoi, L.A. Andritsos, J.S. Blachly, et al., Classic hairy cell leukemia complicated by pancytopenia and severe infection: a report of 3 cases treated with vemurafenib, Blood Adv. 3 (2019) 116–118.