sciendo

Journal of the Australasian Society of Aerospace Medicine (JASAM) No.13 (2024) 9-14
10.2478/asam-2024-0003

HAIRY CELL LEUKAEMIA DIAGNOSED IN A MILITARY AVIATOR

Dr Katrina Francke

Squadron Leader
Aviation Medical Officer (AVMO)
RAAF Institute of Aviation Medicine (IAM)
AMBHC
RAAF Base Amberley

katrina.franke@defence.gov.au

INTRODUCTION

Hairy cell leukaemia (HCL) is a rare type of chronic leukaemia involving B lymphocytes. This case report discusses the diagnosis and management of a military pilot, including the aeromedical considerations for fitness to return to flying duties whilst continuing on prophylactic antiprotozoal agent, pentamidine.

CASE REPORT

A 48 year old Australian Army rotary wing pilot was diagnosed with hairy cell leukaemia following investigation of neutropenia on screening blood tests, as part of his annual aircrew medical.

Review of medical records showed that twenty years earlier he had been diagnosed with chronic neutropenia, with low neutrophil count on repeated routine aircrew medical blood tests. At this time, he was reviewed by a haematologist, and investigations including bone marrow biopsy, showed no underlying haematological pathology. He was commenced on 3-monthly surveillance full blood counts and annual haematologist review.

The patient was stable for many years, before displaying asymptomatic neutropenia two years ago, with repeated low neutrophil counts as low as 0.7 $x10^9$ /L (normal = 2.0-7.5 x 10^9). A diagnosis of chronic idiopathic neutropenia was made, and 3 monthly blood tests were again commenced. A neutrophil count of 0.5 x 10^9 prompted a bone marrow biopsy, which showed the bone marrow to be infiltrated with mature lymphoid cells with hairy cell morphology. CT scan chest, abdomen and pelvis was performed and showed no obvious metastatic disease. There was no significant lymph node enlargement.

A 5 day course of cladribine chemotherapy was given. Pegfilgrastim was given post treatment and daily prophylactic oral valaciclovir, and Bactrim were commenced.

The patient developed red eyes and was seen by an ophthalmologist. The patient was found to have bilateral widespread perilimbal corneal infiltrates, which were presumed to be autoimmune, possibly related to treatment with Bactrim. Bactrim was ceased, and these infiltrates resolved completely with 2 weeks of topical steroid. Nebulised pentamidine was commenced on a monthly basis for antimicrobial prophylaxis, in place of Bactrim.

The patient continued with monthly pathology testing of full blood count, urea and electrolytes, and liver function tests. A repeat bone marrow was performed 4 months post chemotherapy which showed complete disease remission. The patient did not report significant side effects from the ongoing pentamidine, only a short lived unpleasant taste post treatment. Further investigations were conducted to exclude objective evidence of side effects of pentamidine. CXR and spirometry did not show evidence of respiratory infiltrates. ECG was normal. Further blood investigations of serum calcium, blood sugar level, in addition to monthly surveillance full blood count with differentials, urea and electrolytes and liver function tests were normal. The patient had an MRI of his brain to exclude radiological evidence of neurological involvement. There was no significant neuropsychological difficulty noted on review with specialist Neuropsychologist.

The patient returned to flying 6 months post chemotherapy whilst continuing on inhaled pentamidine and oral valaciclovir for a total of 12 months duration. A 24 hour temporary medically unfit for flying (TMUFF) period applied post treatment, to ensure any local acute irritation in his lungs had settled.

He is now 12 months post cladribine, is off chemoprophylaxis, and remains well. His ongoing surveillance is 3-monthly FBC and E/LFT to 2 years, 4-monthly surveillance blood tests to 3 years, and then 6-monthly ongoing. He does have intermittent mild neutropenia, which the specialist is not concerned about with regards to possible HCL relapse, unless his neutrophil count falls persistently lower than 1.0. He is reviewed by his haematologist 6 monthly.

Significant patient medical history includes Graves' disease, which was treated with radioactive iodine 20 years ago. He is stable on Eltroxin 1200mg weekly, and has 3 monthly thyroid function tests and yearly review with an endocrinologist. He also takes fish oil and glucosamine for cervical spondylosis and bilateral chondromalacia patellae, and a probiotic.

DISCUSSION

Disease Overview

Hairy cell leukaemia (HCL) is an uncommon B-cell lymphoproliferative disorder characterised by an accumulation of small mature B cell lymphoid cells with abundant cytoplasm and "hairy" projections within the peripheral blood, bone marrow and splenic red pulp[1]. HCL can present with splenomegaly or cytopenias: - anaemia, thrombocytopenia, and neutropenia with complications of fatigue, bleeding and infection. Roughly a quarter of cases are asymptomatic and are found incidentally[(1)].

HCL represents about 2 percent of all leukaemia and less than 1 percent of lymphoid neoplasms[(1)]. In the USA, there is estimated incidence of 3 cases per million persons per year, with 600-800 new cases each year[(1)]. The median age of onset is 50-55yrs with a male: female ratio of ~4:1[(1)].

The pathogenesis of HCL is incompletely understood[(1)]. 70-90% of cases are thought to arise from a late activated memory B cell that acquires a BRAF V600E gene mutation[(2)]. This leads to enhanced cell survival. Possible causes postulated include exposure to ionising radiation, pesticides and farming[(1)]. Exposure to solvents, alcohol, cigarette smoke and obesity not thought to be risk factors[(1)]. A number of familial cases have been described[(1)].

Diagnosis of HCL is through detection of hairy cells in peripheral blood films or in bone marrow aspirates, together with review of immune-phenotypic profile[(2)]. The disease affects peripheral blood, bone marrow, spleen, liver and lymph nodes. Peripheral blood typically shows a pancytopenic picture, with circulating tumour cells. The bone marrow typically shows HCL-induced marrow fibrosis and the interlocking cell borders of hairy cells[(1)]. Tumour infiltration of the spleen is anticipated in virtually all cases[(1)]. The liver can be involved, but hepatomegaly is rare. Lymph nodes are not typically involved [(1)]. Abdominal lymphadenopathy is associated with poorer response to treatment and reduced overall survival[(3)].

Although not typical, HCL can involve skin, skeletal bone, vascular structures and neurological tissue[(4,5)]. CNS involvement (brain, meningeal, or CSF) is extremely rare, with the majority of cases relating to infection post treatment. There have, however, been a few case studies published of HCL involving brain parenchyma[(4,6)]. Perry et al. published a case study in 2017 of a 42 year old gentleman who presented with a 4 month history of headaches, fatigue, shortness of breath and easy bruising[(6)]. Investigations revealed a diagnosis of HCL. Brain imaging with CT and MRI scans demonstrated what appeared to be innumerable small acute microhemorrhages in multiple areas of the brain including both cerebral and cerebellar hemispheres and brain stem. Brain biopsy showed evidence of HCL infiltration.

A similar case study was published by Chandana et al. in 2013[(4)]. Here, a 51 year old male presented with 1 week history of confusion and word finding difficulties. Patient work up revealed a diagnosis of HCL with multifocal brain parenchymal involvement on biopsy in the form of intracerebral hemorrhages with abnormal lymphocytes[(4)]. Another unusual case of HCL published by Chai et al. in 2017 describes a 68 year old male who presented solely with the psychiatric symptom of delusions[(5)]. Patient work up revealed involvement of multiple atypical sites, including skeletal bone, and brain parenchyma, without involvement of peripheral blood or spleen[(5)]. Chaudrey et al. describe a case of HCL presenting as a cranial mass in a 42 year old male[(7)]. Workup revealed disseminated disease, with splenomegaly, widespread lymphadenopathy, soft tissue masses and skeletal involvement.

Disease Management

Many patients with HCL are asymptomatic and can be observed for extended periods of months or years after diagnosis before requiring treatment[(8)]. These patients can be observed 3-6 monthly due to the slow course of this tumour. Medical review entails review of general health, screening for constitutional symptoms, examination for splenomegaly or adenopathy, and laboratory studies screening for cytopaenias or reappearance of hairy cells in the peripheral blood, or bone marrow[(8)].

Treatment is warranted when there are significant cytopaenias (peripheral blood neutrophil count <1000/microL, haemoglobin < 11 g/dL, or platelet count

< 100,000/microL), symptomatic splenomegaly or adenopathy, or constitutional symptoms (fever, night sweats, fatigue, weight loss)[8].

Chemotherapy with purine analogues is the mainstay of treatment, with a single course of treatment using purine analogue cladribine or Pentostatin[2]. No randomised controlled trials have compared both drugs and there is no evidence in the literature to indicate superiority of one drug over the other[2]. Prior to the use of these agents in the 1980's, median survival was reported as 4 years[1]. Cladribine (2-chlorodeoxyadenosine) is often used as first line treatment, due to the ease of its administration, with shorter duration of therapy and general tolerability[1]. Cladribine targets lymphocytes and is cytotoxic to both resting and dividing cells, through inhibiting DNA synthesis and repair [9].

Treatment for HCL is not curative, but aims for remission. Patients will typically have periods of remission before episodic return of disease. The rate of complete remission and the length of disease free survival become progressively shorter with each relapse[10].

Remission can be partial or complete. Assessment of response is evaluated with a physical examination, full blood count and bone marrow biopsy, done at 4-6 month post treatment[1]. A complete response is defined by normalisation of peripheral blood counts, resolution of palpable splenomegaly and disappearance of hairy cells from bone marrow[1]. In these patients, survival is prolonged to a near normal lifespan[11]. Partial remission is defined by having minimal residual disease, with HCL infiltrates recognisable by immunohistochemical stain for CD20 but not by conventional stains[1]. Partial remission can lead to possible earlier relapse, but these patients may remain asymptomatic for many years without the need for further therapy[1].

Patients treated with cladribine require chemoprophylaxis to prevent opportunistic infections secondary to their immunocompromise. Pneumocystis jirovecii is an opportunistic organism capable of causing pneumonia in immunocompromised patients, whether due to malignancy, organ transplantation or human immunodeficiency virus (HIV). Bactrim (trimethoprim / sulfamethoxazole) is the first line antimicrobial used to prevent pneumocystis jirovecii pneumonia (PJP), with pentamidine a suitable alternative for patients who cannot tolerate Bactrim. In HIV positive patients, the risk of PJP is strongly correlated with decreased CD4 cell count [12]. CD 4 counts in non HIV immunocompromised patients is less well studied, but a systematic review published in 2017 on this patient population aligned with recommendations in HIV positive patients[13]. Namely, when CD4 counts fall to 200 cells per microliter or less, prophylaxis for PJP is recommended. CD4 counts above 200 cells per microliter for more than three months are recommended prior to ceasing prophylaxis[13].

Patient specific treatment:

Cladribine was the purine analogue used to treat HCL in this patient. Common adverse effects (>1%) include fever, myelosuppression, headache, dizziness, nausea, vomiting, diarrhoea, constipation, abdominal pain, oedema, cough, myalgia, arthralgia. Haemolytic anaemias occur infrequently (0.11%), and rarely (<0.1%) there can be renal impairment, pulmonary interstitial infiltrates, alterations in LFTs and neurotoxicity[9]. There is risk of teratogenicity, and contraception needs to be used in both men and women for treatment and for 6 months after dose[14]. It is Class D medication. It is 12 months post treatment.

Pegfilgrastim is a G-CSF (granulocyte colony stimulating factor) which stimulates production and differentiation of neutrophils from blood precursor cells, shortening the period of neutropenia. The most common side effect of G-CSF's is bone pain, experienced in ~20% of patients having daily GCSF[15]. Paracetamol and NSAIDS are the first line agents to treat this bone pain. It is 11 months post treatment.

Valaciclovir is prescribed for HSV and VZV prophylaxis. There is nil impact on fitness to fly with each use, once ground trial of 3 days has been completed, as per the Australian Defence Force (ADF) Medication list for Aircrew guidelines **(reference)**.

Eltroxin – As per the ADF Medication list for Aircrew, there is a ground trial period for a minimum of 28 days initially, with 7 days grounding with each subsequent dose change.

Pentamidine is a broad spectrum anti-microbial agent that can be prescribed for prophylaxis of Pneumocystis jiroveci (carinii) pneumonia[17]. The mode of action is not fully understood and it is thought to interfere with microbial RNA/DNA, phospholipids and protein synthesis through the inhibition of oxidative phosphorylation and/or interference with incorporation of nucleotides and nucleic acids into RNA and DNA effects on folate metabolism[1,17]. Pentamidine is as effective as, but generally more toxic than trimethoprim with sulfamethoxazole for prophylaxis or treatment of pneumocystis carinii [17].

Pentamidine can be given intravenously or via inhalation. For the prevention of PCP, 300mg nebulised pentamidine is used every 4 weeks. Inhaled pentamidine is found in high concentration in bronchoalveolar fluid. The systemic absorption of pentamidine is thought to be limited with repeated inhalation therapy, however the extent and consequence of this accumulation is unknown[18]. Following inhalation, pentamidine is rarely detectable in the plasma, but bronchoalveolar concentrations are 5-10 times higher than with IV administration[19]. Patients receiving inhaled pentamidine should be closely monitored for development of serious adverse

reactions that have occurred in patients with parenteral pentamidine[18].

Adverse effects with parenteral pentamidine are common, including reversible nephrotoxicity, acute hypotension, pancreatitis, elevated liver enzyme concentrations, hypoglycaemia, blood disorders and arrhythmias[20,21]. Fatigue, dizziness, nausea, vomiting, diarrhoea, taste disturbance, eye discomfort, rash, toxic epidermal necrolysis, eosinophilia pneumonia, dizziness, headache, blurred vision, anxiety, depression, chest pain, hypoglycaemia and pancreatitis have also been reported[17,18].

Inhaled pentamidine is much less toxic than parenteral administration, due to its limited systemic absorption, but commonly causes cough and bronchospasm, sore throat, oral paraesthesia and a metallic taste[17,21]. Hypokalaemia and hypomagnesaemia, pancreatic toxicity, unpleasant taste in the mouth, GI disturbances, maculopapular rash, pneumothoraces and hallucinations have been reported with inhaled pentamidine[19,21]. Hypoglycaemia and less often, hyperglycaemia may occur even after stopping treatment[17], with no indication as to the length of time implicated.

The patient has received multiple treatments of nebulised pentamidine, with isolated short term side effect of an unpleasant taste in his mouth.

Prognosis:

A good review of published data is found in the *Hairy cell leukaemia: 2020 update on diagnosis, risk stratification, and treatment,* published in American Journal of Hematology[2]. In two large retrospective series with roughly 1600 patients in total, complete response was seen in 76-83% of patients, and partial response in 31-33% of patients with nil significant difference found between using cladribine or pentostatin[2, 22, 23, 24]. There was no long-term follow-up showing a plateau in failure-free survival. Roughly half the patients relapsed in the first 5 years after treatment. These patients were more difficult to treat, and are at higher risk to have decreased overall long term survival. In patients with remission over 5 years, further treatment with purine analogues can be as effective as second-line therapy. Chemoimmunotherapy, using cladribine followed by Rituximab, an anti-CD20 antibody was recommended as an option for patients with relapse at 2-5 years, with 100% failure free survival and overall survival of 100% in a study of 14 relapses cases. Chemoimmunotherapy has also been trialled in initial therapy with promising results[25] and now alongside chemotherapy is a first line option for symptomatic patients with HCL[2]. Patients relapsing before 2 years require confirmation of HCL diagnosis[2].

Patients with HCL have an increased incidence of secondary malignancies, most notably in haematological malignancies, particularly non-Hodgkin lymphomas and Hodgkin lymphomas[2]. Data from worldwide cancer registries and studies show a cumulative incidence varies from 5% to 32% depending on time of follow up[2]. Observed-to-expected ratios of second malignancies is generally increased, ranging from 1.01 (CI95% 0.74-1.33) to 1.88(95%CI 1.24-2.74)[2].

This increased risk can be related to the disease and/or the treatment and the role of cladribine in the development of secondary malignancies remains debatable[2].

AEROMEDICAL CONSIDERATIONS

This is a case of an experienced military rotary wing pilot with 22 years flying experience and 2,760 flying hours in total. He is in complete remission for HCL, and is no longer on any prophylactic medication and remains asymptomatic. He returned to flying duties whilst on valaciclovir and pentamadine and with the caveat that he fly as or with a co-pilot.

Aeromedical considerations for return to flying duties include risk of disease recurrence, risk of sudden incapacitation and subtle incapacitation if relapse occurred, possible treatment side effects and their impact on flying duties, ability to safely control the aircraft and the ability to egress rapidly in an emergency, and potential of increased risk to the member in the aviation environment.

Risk of recurrence: Treatment for HCL is not curative and recurrence of disease is expected. Due to the slowly progressing nature of HCL, periodic monitoring for fall in neutrophil count will give an early indication of possible disease recurrence.

Risk of sudden incapacitation: The risk of sudden or subtle incapacitation from disease relapse is low. Disease manifests in cytopaenias, splenomegaly, or recurrent infections. This is very unlikely to cause sudden incapacitation. Secondary malignancies, although increased in incidence in this population, are still very uncommon and if present, are unlikely to lead to sudden incapacitation of the patient. Malignancies are typically haematological and are screened for whilst monitoring for relapse of HCL.

Neurological involvement is rare in HCL, with only a handful of cases reported. Naturally, the concern with neurological involvement is the risk of sudden incapacitation from seizure. Cranial imaging in the form of an MRI was completed in this aviator, and showed no abnormality.

Neuropsychology review was conducted, with no indication of any significant neuropsychological difficulty on assessment. There was adequate performance on tests of effort and application.

Treatment side-effects: There have been no significant side effects from the medication and there is no evidence of end organ damage.

Aircraft control and egress are unaffected.

Aircraft environment: The aviation environment and stressors of flight are not expected to affect the member beyond other crew members, or adversely impact on recurrence of his disease.
Military Medical classification: This pilot has been made MEC J31 SPEC A2(1-7, 1-8, 1-9, 1-10, 2-19, 4-1, 4-2, 4-3, 4-11, 6-3, 6-6). Restrictions include the need to fly as or with co-pilot in a multicrew environment, and requiring 24 hours medically unfit for flying after pentamidine use, and the need for ongoing surveillance under the care of a haematologist to detect early disease recurrence, and consequently limiting flight safety issues.

CONCLUSIONS

Hairy cell leukaemia is a rare condition in the general population, and likewise, so too in aviators. With this aviator in complete remission, critical review of the literature has supported the aeromedical decision for an early return to flying, whilst continuing on inhaled pentamidine. Disease recurrence is almost guaranteed, however, through robust surveillance combined with the slow progressive nature of the disease, the risk of sudden incapacitation can be mitigated. Furthermore, flying as or with copilot further mitigates risk in the aviation environment.

DISCLAIMERS

This manuscript has been approved by JHC for public release IAW Defence Medica and Communication Policy and JHC administrative guideline.

The patient has consented to submission of this case review.

REFERENCES

1. UpToDate. Hairy Cell Leukaemia. https://www.uptodate.com/contents/clinical-features-anddiagnosis-of-hairy-cell-leukemia? accessed online May 26 2020

2. Maitre E, Cornet E, Troussard X. Hairy cell leukemia: 2020 update on diagnosis, risk stratification, and treatment. *Am J Hematology Vol 94, issue 12, Dec 19 Pg 1413-1422*. https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.25653

3. Mercieca J, Purga M, Matutes E et al. Incidence and significance of abdominal lymphadenopathy in hairy cell leukaemia. Leukaemia & Lymphoma. 1994; 14 Suppl 1:79-83. https://europepmc.org/article/med/7820058

4. Chandana SR, Kotecha R, Al-Janadi A et al. Rare case of hairy cell leukemia with brain parenchymal involvement: a diagnostic dilemma. J Clin Oncol. 2013; 31:e186-e8 accessed online ascopubs.org/doi/pdf/10.1200/JCO.2012.44.8787

5. Chai KL, Morris T, Bazargan A. A Case Report of Hairy Cell Leukemia: An Unusual Presentation. Ann Clin Case Rep 2017; 2:1412 scopubs.org/doi/pdf/10.1200/JCO.2012.44.8787

6. Perry A, Matsua K, Wadhwa V et al. Multifocal brain involvement in a patient with hairy cell leukemia successfully treated with rituximab and cladribine. Blood Adv. 2017 Jun 13; 1 (14): 899-902. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5737593/

7. Chaudrey MS, McDonald D, Stirickland N. Hairy cell leukemia presenting as a cranial mass. Am J Hematol. 2011; 86: 423-424. scopubs.org/doi/pdf/10.1200/JCO.2012.44.8787

8. UpToDate. Treatment of hairy cell leukaemia. https://uptodate.com/contents/treatmen-of-hairycell-leukaemia? accessed online June 01 2020

9. Australian Medicines Handbook. Cladribine. Website https://amhonline.amh.net.au/chapters/immunomodulators-antineoplastics/cytotoxicantineoplastics/antimetabolites/cladribine accessed online 19 May 2020

10. Else M, Dearden C, Matutes E et al., Long-term Follow-Up of 233 Patients With Hairy Cell Leukaemia, Treated Initially With Pentostatin or Cladribine, at a Median of 16 Year From Diagnosis. Br J Haematol.2009 Jun;145(6):733-40. https://pubmed.ncbi.nlm.nih.gov/19344416/

11. Divino V, Karve S, Gaughan A, et al. Characteristics and treatment patterns among US patients with hairy cell leukemia: a retrospective claims analysis. *J Comp Eff Res.* 2017;**6**:497508.https://www.futuremedicine.com/doi/full/10.2217/cer-2017-0014?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed&

12. UpToDate. Overview of prevention of opportunistic infections in HIV-infected patients. https://www.uptodate.com/contents/overview-of-prevention-of-opportunistic-infections-in-hivinfected-patients Accessed 21 Jul 20

13. Messiaen E, Cuyx S, Dejagere T, et al. The role of C 4 cell count as discriminatory measure to guide chemoprophylaxis against *P neumocystis jirovecii* pneumonia in human immunodeficiency virus-negative immunocompromised patients: A systematic review. Transpl Infect Dis. 2017;19:e12651 https://doi.org/10.1111/tid.12651

14. drugs.com. website https://www.drugs.com/sfx/cladribine-side-effects.html accessed online 24 May 2020

15. Lambertini M, Del Mastro L, Bellodi A, Pronzato P. The five "Ws" for bone pain due to the administration of granulocyte-colony stimulating factors (G-CSFs). Crit Rev Oncol Hematol. 2014 Jan;89(1):112-28. https://www.sciencedirect.com/science/article/abs/pii/S1040842813001832

16. ADF Medication list for Aviation-Related Occupations, Document version 6, 16 Dec 2019. Pages - Health Care Tools and Guidance (defence.gov.au)

17. Australian Medicines Handbook. Pentamidine. website https://amhonline.amh.net.au/chapters/anti-infectives/antifungals/other-antifungals/pentamidine accessed online 24 May 2020

18. UpToDate. Pentamidine (oral inhalation): Drug information. https://www.uptodate.com/contents/pentamidine-oral-inhalation-drug-information?. Accessed 1 Jun 20

19. Monk J, Benfield P. Inhaled pentamidine. An overview of its pharmacological properties and a review of its therapeutic use in Pneumocystis caring pneumonia. Drugs 39, 741-756 (1990)

20. Therapeutic Guidelines. Practical information on using pentamidine. Published Apr 2019. Accessed online 10 June 2020. https://tgldcdp.tg.org.au/viewTopic?topicfile=using-antifungaldrugs&guidelineName=Antibiotic#toc_d1e164

21. UpToDate. Antiprotozoal therapies. https://www.uptodate.com/contents/antiprotozoal-therapies? Updated March 2019, Accessed 1 Jun 20.

22. Cornet E, Tomowiak C, Tanguy-Schmidt A et al. Long-term Follow-Up and Second Malignancies in 487 Patients With Hairy Cell Leukaemia. Br J Haematol. 2014 Aug; 166 (3):390400.https://pubmed.ncbi.nlm.nih.gov/24749839/

23. Else M, Dearden CE, Catovsky D. Long-term follow-up after purine analogue therapy in hairy cell leukaemia. Best Prac t Res Clin Haematol. 2015; 28:217-229. https://www.sciencedirect.com/science/article/pii/S152169261500016X

24. Dearden CE, Else M, Catovsky D. Long-term results for pentostatin and cladribine treatment of hairy cell leukemia. Leuk Lymphoma. 2011;52:21-24. https://www.tandfonline.com/doi/abs/10.3109/10428194.2011.565093

25. Chihara D, Kantarjian H, O'Brien S, et al. Long-term durable remission by cladribine followed by rituximab in patients with hairy cell leukaemia: update of a phase II trial. *Br J Haematol*. 2016;**174**:760-766. https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.14129