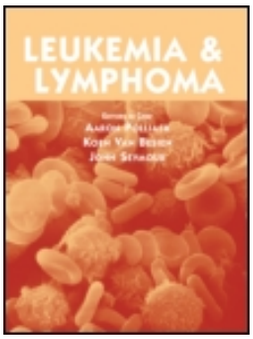

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

More than a feeling: new approach required for assessing immunosuppression

Benjamin W. Teh & Monica A. Slavin

To cite this article: Benjamin W. Teh & Monica A. Slavin (2014) More than a feeling: new approach required for assessing immunosuppression, Leukemia & Lymphoma, 55:5, 975-976, DOI: 10.3109/10428194.2013.867491

To link to this article: https://doi.org/10.3109/10428194.2013.867491

Leukemia & Lymphoma, May 2014; 55(5): 975–976

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2013.867491

informa
healthcare

COMMENTARY

More than a feeling: new approach required for assessing immunosuppression

Benjamin W. Teh[1] & Monica A. Slavin[1,2]

[1]*Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Australia and* [2]*Victorian Infectious Diseases Service, Royal Melbourne Hospital, Parkville, Australia*

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world. Despite advances in treatment and survival seen in the past decade, infective complications are a significant cause of morbidity and mortality in patients with CLL, with infection related mortality ranging from 30 to 50% [1]. This stems from multiple disease and treatment related factors. Disease related impairment of the immune system is well known, and involves multiple arms of the immune system including hypogammaglobulinemia and numerical and functional deficits of T lymphocytes, monocytes and neutrophils, compounded by defects in the level and activity of complement [2,3]. Infection risk increases with duration and stage of disease. Unsurprisingly, the pattern of infections seen with or without treatment with alkylating agents consists mainly of infections with encapsulated bacteria [2].

The introduction of various treatment regimens has added to the pre-existing disease related immunosuppression. Although purine analogs have led to significantly improved disease response rates, they have also resulted in a change in the incidence and spectrum of infections through selective depletion of CD4 T lymphocytes for as long as 2 years [3]. In addition to bacterial infections, previously unseen opportunistic infections such as *Pneumocystis jirovecii* and *Listeria monocytogenes* and reactivation of latent viral infections have been increasingly detected in this patient group [4]. It should be noted that with successful disease treatment and remission, the risk of severe and opportunistic infections declines with increasing length of remission [5].

Purine analogs such as fludarabine are now used in combination with cyclophosphamide and rituximab (FCR) as first-line therapy. While the addition of rituximab to fludarabine and cyclophosphamide has not led to an overall increased incidence of infections, rare and often fatal viral infections such as JC virus-associated progressive multifocal leukoencephalopathy have been associated with rituximab use [2]. In this issue, Appleby *et al.* describe two patients with CLL managed with FCR who presented with febrile episodes in association with high detectable BK viral loads in urine [6]. BK virus belongs to the same polyomavirus family as JC virus. High BK viral load was associated with hemorrhagic cystitis in one of the cases, while the other had symptoms of cystitis. Although not heavily pretreated, both cases had significant burden of disease. BK virus related hemorrhagic cystitis is uncommonly seen outside of transplant recipients, and is a marker of severe and profound immunosuppression.

Purine analogs used in combination therapy for salvage treatment are associated with a further increased risk of infection compared to first-line therapy, highlighting refractory disease and multiple treatment courses as risk factors for infection [2,7]. Cumulative immunosuppression results from a contribution of progressive or refractory disease and treatment related factors, but this is often difficult to assess. Lessons learnt from past studies have resulted in the use of prophylaxis such as trimethoprim–sulfamethoxazole against *Pneumocystis* and *Listeria*, and the use of acyclovir against reactivation of herpes viruses for patients managed with fludarabine or monoclonal antibodies such as alemtuzumab [3,8]. For some infections such as the cases presented by Appleby *et al.*, prophylaxis has not proven feasible. Although prophylaxis reduces the rates of some infective complications such as *Pneumocystis* or herpes viruses, the duration of prophylaxis required has remained largely undefined. There is some evidence that the commonly practiced duration of prophylaxis of several months after ceasing treatment may not be adequate, due to longer than expected persistence of immunosuppression [9].

In patients with CLL, there is interplay between disease, treatment related immunological deficits and consequent risk and patterns of infection [2,3]. However, it is not always clear why some develop more serious and rare infections than others. This provides an opportunity for the use of immunological profiling to determine depth of immunosuppression and thus predict infective risk. Purine analogs, the current standard treatment for CLL, are known to deplete T lymphocytes. This depletion of T lymphocytes is thought to contribute to the range of opportunistic infections

Correspondence: Monica A. Slavin, Department of Infectious Diseases, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street, Melbourne, 8006, Australia. Tel: + 613-9656-1156. Fax: + 613-9656-1185. E-mail: monica.slavin@petermac.org

This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

seen [4,5]. Correlation between CD4 cell counts and opportunistic infection risk and type has been long established in the human immunodeficiency virus (HIV) positive patient population [10]. While this correlation is not as well described in the hematology population, there is evidence, when CD4 counts are reported, that opportunistic infections such as *P. jirovecii* occur in association with CD4 counts <200 cells/μL in patients managed with FCR [9]. Future studies of opportunistic infective complications should consider reporting CD4 cell counts where available, to help define this association.

Improved survival afforded by therapies for CLL will result in a large group of patients maintained by multiple lines of treatment with cumulative immunosuppression. In our opinion, monitoring of CD4 cell counts in patients with CLL managed with purine analogs and/or alemtuzumab may aid the identification of "at risk" patients and help guide commencement and duration of prophylaxis. The management of infective complications in HIV-positive patients has shown that CD4 guided prophylaxis management is practical and effective [10]. However, the utility of this approach in the hematology population, as well as the incorporation of more complex immunological profiling such as quantification of T cell responses to pathogenic antigens, will require further study, correlation with epidemiological studies of infective complications and clinical validation, before it can be considered standard practice.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Molica S. Infections in chronic lymphocytic leukemia: risk factors, and impact on survival, and treatment. Leuk Lymphoma 1994;13:203–214.

[2] Nosari A. Infectious complications in chronic lymphocytic leukemia. Mediterr J Hematol Infect Dis 2012;4:e2012070.

[3] Morrison VA. Management of infectious complications in patients with chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2007:332–338.

[4] Byrd JC, Hargis JB, Kester KE, et al. Opportunistic pulmonary infections with fludarabine in previously treated patients with low-grade lymphoid malignancies: a role for Pneumocystis carinii pneumonia prophylaxis. Am J Hematol 1995;49:135–142.

[5] Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112: 975–980.

[6] Appleby N, Dillon A, Arrigan M, et al. Symptomatic BK virus reactivation following fludarabine, cyclophosphamide and rituximab chemotherapy for chronic lymphocytic leukemia/small lymphocytic lymphoma. Leuk Lymphoma 2014;55:1181–1183.

[7] Molteni A, Nosari A, Montillo M, et al. Multiple lines of chemotherapy are the main risk factor for severe infections in patients with chronic lymphocytic leukemia with febrile episodes. Haematologica 2005;90:1145–1147.

[8] Thursky KA, Worth LJ, Seymour JF, et al. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab*. Br J Haematol 2006;132:3–12.

[9] Haeusler GM, Slavin MA, Seymour JF, et al. Late-onset Pneumocystis jirovecii pneumonia post-fludarabine, cyclophosphamide and rituximab: implications for prophylaxis. Eur J Haematol 2013;91: 157–163.

[10] Kaplan JE, Benson C, Holmes KH et al.; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58(RR-4):1–207.