Risk of thromboembolism with lymphoma: myth or reality?

Kate L Burbury[1], Marliese Alexander[1,2], David A Westerman[1,3]

[1]Division of Cancer Medicine, Peter MacCallum Cancer Centre, East Melbourne, Melbourne, Australia. Monash University, [2]Melbourne, Victoria, Australia. [3]University of Melbourne, Parkville, Victoria, Australia

Correspondence to:

Dr Kate Burbury

Peter MacCallum Cancer Centre

Locked Bag 1 A'Beckett Street

Victoria 8006 Australia

Ph: +61 3 9656 1076

Fax: +61 3 9656 1408

kate.burbury@petermac.org

Words: 1245

Despite the availability of safe and efficacious antithrombotic agents, as well as the vast clinical experience justifying their use, thromboembolism (TE) remains a frequent complication among cancer patients, with substantial adverse health and economic consequences.[1] Cancer-associated thrombosis remains an important negative predictor of survival as well as a leading cause of death, and is associated with higher (2-3 fold) TE recurrence rates, higher (2-6 fold) bleeding complications on anticoagulant therapy, increased hospitalisation and impaired quality of life.[2,3] Moreover, an incident TE event, once a cancer has been diagnosed and treatment started, often denotes a significant clinical hurdle, not only related to the morbidity and mortality associated to the TE event, but also the potential detrimental effect of an interruption or modification in therapy, attributable to the event and/or delivery of therapeutic anticoagulation. As such, risk-adapted primary thromboprophylaxis can have a substantial impact not only on TE reduction, but also disease response, survival, quality of life and healthcare resources. Much of the focus regarding prevention of cancer-associated TE has been with solid malignancies. However, recent studies, including Borg *et al* in this issue of ***Leukaemia and Lymphoma***, have demonstrated that the risk of TE in patients with non-Hodgkins lymphoma (NHL) is clinically relevant and that in appropriately risk-stratified populations, the observed risk is potentially comparable to other high TE risk subgroups.[4-12]

In retrospective studies and pooled analyses the reported incidence of TE among patients with NHL varies substantially from 1-15%. This variability in reported risk is largely due to the heterogeneity in patient- and tumour-related factors (as well as therapy administered), with high grade lymphoma, such as diffuse large B-cell - including primary CNS and mediastinal lymphoma - conferring the highest rates.[5-7,10,11,13] A few prospective studies have equally demonstrated higher TE rates in DLBCL. [14,15] This burden of

disease may well be underestimated, given the focus is generally on clinical macrovascular events and as such, under-appreciates the haemostatic, endothelial and inflammatory dysfunction that occurs at a microvascular level, which may still contribute to disease biology, morbidity and mortality.

Risk stratification and predictive modeling tools, can be important enablers to facilitate the design of better targeted management strategies, to improve patient outcomes. Appropriate pharmacological thromboprophylaxis (P-TP) can reduce the rates of TE in up to 80% of at-risk patients, but this needs to be balanced against the potential serious complication of bleeding. Therefore the ability to identify patients, and the duration of risk, will allow a more personalised risk-directed approach, rather than the broad application in patients with lymphoma.

Importantly, in all reported studies, the majority (>90%) of TE events among patients with NHL occur early, generally within 3 months from diagnosis, and during therapy.[4,8,9,12,13] The risk appears greatest in those patients with higher grade disease (i.e. DLBCL vs low grade lymphoma), primary CNS lymphoma, prior TE, more advanced stage disease, extra-nodal sites, increased BMI (>30kg/m^2) and reduced performance status (ECOG 2-4).[4-9,11,12,15] Although this current study recognised only ECOG 2-4, advanced stage disease and prior TE event as predictors in multivariate analysis. An important limitation of this current study, and many studies to date, is the retrospective design and the limitation of source data to provide accurate assessment of proposed risk factors.

Thrombosis Lymphoma (ThroLy) score was developed as a predictive tool for TE among patients with lymphoma and was derived from large cohort of patients with NHL (n=1820). The score consists of variables, clinical parameters and modified Khorana parameters, which based on regression coefficients from a multivariate analysis, assigned 2 points for all parameters with an OR >5 (previous TE events, mediastinum involvement, and BMI) and 1 point for all remaining significant variables. The TE risk categories based on the score: low (0-1), intermediate (2-3) and high (> 3), had a positive predictive value (probability of TE in those designated high risk) of 65.2%, but demonstrated limited predictive stratification otherwise.[4] Moreover, given the purpose of a risk prediction tool is to achieve a high sensitivity (or predictive capacity) for patients at potential risk, there is a strong need for improvement.

So how can we better predict risk in our patients, both at diagnosis and as they embark on their potentially curative therapeutic regimens? Firstly, understanding the pathophysiology will facilitate a more directed preventative strategy, in terms of the most appropriate pharmacological agent and schedule, given there is now a growing number of antithrombotic agents available for consideration. Secondly, defining clinically relevant and practical biomarkers, that provide both potent and feasible risk stratification, which can be applied in a simple algorithm, real-time, for appropriate decision-making. Thirdly, the longitudinal (or sequential) assessment of biomarkers, to investigate both the impact of therapy on TE risk and more importantly, the duration of risk, given the dynamic nature of the patients TE risk during their disease and treatment journey – which was also demonstrated by Borg *et al*. A further pivotal point to reinforce relates to the significant under prescription of thromboprophylaxis for high risk patients in the ambulatory setting. It was in 2008 that the US Surgeon General “called to action to prevent TE”. Significant improvement has been

achieved through the implementation of systems for routine inpatient thromboprophylaxis, however the ambulatory setting remains an under-recognised problem, requiring greater endeavours in the high risk cohort.[16,17]

Khorana *et al*, and others, have demonstrated the utility of incorporating thrombogenic biomarkers to predict TE risk in cohorts of patients with various cancers.[18] Combination markers, built into a risk assessment model (RAM), have demonstrated predictive power across populations. However in lymphoma this has been predominantly in hospitalised patients, whereas the majority of patients are managed in the ambulatory care setting. Moreover these studies have measured the biomarkers at baseline only. Nevertheless, the use of Khorana prediction tool provides some insight into the potential application of RAM. A pooled data analysis of 12 frontline clinical trials from Fondazione Italiana Linfomi (n=1,184 lymphoma patients assessable by the Khorana score), demonstrated that intermediate-high Khorana score was predictive for symptomatic TE.[9]

However, while biomarkers have been shown to be predictive for *index* TE events, risk-adapted primary prophylaxis based on these scoring systems is yet to be prospectively assessed in clinical studies. More importantly, currently proposed biomarkers, such as P-selectin, Prothrombin fragments 1+2, thrombin generation assays, lack widespread clinical availability and standardisation, which makes implementation into daily practice difficult.

Despite the shortcomings of studies to date, TE rates among lymphoma patients do warrant further attention. Understanding the major haemostatic dysfunction, as well as mapping the

heterogeneity in TE risk for patients with lymphoma, and indeed other cancers, is pivotal for developing robust decision-making algorithms for the prevention of cancer-associated TE. The risk is likely to be dynamic, particularly throughout the administration of therapy and disease response. Thus, the prospective longitudinal assessment at strategic time points is likely to provide greater insight into the pathophysiology as well as the risk profiles. Equally utilising relevant, but routinely available and standardised laboratory assays, such as D-dimer, fibrinogen, platelet count (for example), but as continuous variables rather than dichotomised thresholds is likely to be more pragmatic and clinically relevant.[19] Such research could culminate in a simple interface (smartphone and/or tablet APP) which combines key clinical and laboratory parameters that are routinely available, which allows for real-time personalised assessment in the clinic. The APP would provide a simplified risk assessment tool and decision-making algorithm, with guidance and recommendations for the most appropriate TE preventative strategy, in terms of regimen, duration and cautions - and could be extrapolated across various cancer populations and anti-cancer treatment paradigms.

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