EDITORIAL

Understanding risks and refining strategies for thromboembolism prophylaxis in hematopoietic stem cell transplant recipients

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The topic of thromboembolic (TE) risks in hematopoietic stem cell transplant (HSCT) recipients is relatively unexplored, and there is general paucity of randomized controlled trial (RCT) data on reduction of TE complications, as well as risk-adapted prophylaxis approaches in both autologous and allogeneic HSCT patients.

Lee et al. in their study present the data from a single-center retrospective cohort on pre- and post-VTE prophylaxis protocol (VPP) incorporation in HSCT recipients, with primary endpoint being the incidence of composite bleeding events (major bleeding, clinically relevant non-major bleed, and minor bleeding events) and secondary endpoint the incidence of hospital acquired VTE, with a sub analysis of central venous catheter-associated VTE [1].

Prior efforts have pointed out that during HSCT, venous thromboembolism (VTE) is primarily catheter-related and three-fold less common than clinically significant bleeding [2]. Subsequent studies have found that low molecular weight heparin (LMWH) does not decrease the incidence of catheter-associated thrombosis in cancer patients [3]. Nevertheless, it should be highlighted that many hematologic malignancies carry a significant risk of VTE, particularly in the early period from diagnosis: aggressive lymphomas have about 10–15% incidence rate of VTE in the first year, while earlier intensive combinational treatments in newly diagnosed multiple myeloma (NDMM) that incorporated thalidomide and HSCT yielded VTE rates as high as 34% in the immunomodulatory drug (IMiD) group, and remained at 24% despite the protocol amendment that added prophylactic-dose LMWH, raising a question regarding the need for even full dose, risk-adapted anticoagulation during early disease periods [4–6]. Lastly, while recent insights from major RCTs in both transplant eligible and transplant ineligible NDMM suggested that nearly all events occurred within six months of treatment initiation (regardless of treatment regimen) [7], data from post hoc analysis of VTE events in randomized phase 2 GRIFFIN study demonstrated not only unacceptably high VTE incidence rates in both arms [15.7% in lenalidomide, bortezomib and dexamethasone (RVd) vs 10.1% in Daratumumab-RVd (D-RVd) cohorts], but that the median time to the first onset of VTE was longer than expected in the modern, frequently utilized quadruplet regimen such as D-RVd (305 days vs 119 days in RVd triplet) [8]. This is relevant, as in both pre- and post-VPP cohorts by Lee et al., nearly two thirds of patients had antecedent MM, amyloidosis or non-Hodgkin lymphoma before their HSCT (63% and 65%, respectively), and vast majority of patients in both pre- and post-VPP cohorts were also on some form of IMiDs (lenalidomide or pomalidomide) within six months of HSCT (83% and 91%, respectively) [1].

While the process of HSCT is associated with significant periods of high grade thrombocytopenia, thromboembolism is generally possible at any platelet count, with some large cohort studies reporting that up to 44% of VTE events occurred at platelet counts $< 50 \times 10^9$/L in patients undergoing HSCT [2]. Importantly, VTE often occurs at platelet counts generally considered safe for anticoagulation prophylaxis ($\geq 50 \times 10^9$/L), and in the absence of other clear contraindications to anticoagulation. As pointed out by Lee et al., patients in their study were not restarted on thromboprophylaxis when platelets recovered to $> 50 \times 10^9$/L, making it difficult to assess the full impact of their post-VPP measures, considering variable exposure to anticoagulation [1]. This is analogous to an overarching issue of suboptimal utilization of VTE thromboprophylaxis by practitioners, as VTE prophylaxis is unfortunately not routinely incorporated for all patients with hematologic malignancies. A real-world evaluation as well as RCTs in NDMM for example highlight this issue very well, with low number of patients receiving appropriate prophylaxis at the time of VTE, even while receiving care at academic centers [8, 9]. It is worth noting that most of VTE events in the post-VPP group occurred while patients were off VTE prophylaxis, including in those with line-associated VTE, however it remains unclear if those patients had any clear contraindications to VTE prophylaxis at the time of VTE events [1].

We currently do not have evidence-based recommendations for best reduction approaches in the incidence, morbidity and mortality of both venous and/or arterial peri-HSCT TE complications. The current practice guidelines on prevention and treatment of VTE in cancer patients from the American Society of Hematology, American Society of Clinical Oncology and National Comprehensive Cancer Network all provide moderate strength recommendations against routine VTE prophylaxis in HSCT recipients, or no clear recommendations (Table 1) [10–12]. These recommendations are mostly based on expert opinions and/or informal consensus, as availability and/or quality of evidence is insufficient at present, due to critical lack of RCT data that demonstrate safety, efficacy and benefit in this space.

Lee et al. notably found no significant difference in composite bleeding events with respect to VTE prophylaxis intervention, suggesting that it did not pose additional bleeding risk in their HSCT patients, importantly also with a trend towards reduction in VTE [1]. It should also be pointed out that in both pre- and post-VPP cohorts, significant number of patients were autologous HSCT recipients (70% and 74%, respectively), and only minority of patients had non-line associated VTE in both groups (2.9% and 1.5% vs 5.8% and 4.5% in pre- and post-VPP groups, respectively) [1].

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Table 1. Existing recommendations for venous thromboprophylaxis in hematopoietic stem cell transplant recipients by ASCO, ASH and NCCN.

Relevant bodies	Recommendations	Reference
American Society of Clinical Oncology (ASCO)	"*Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion nor to patients undergoing stem-cell/bone marrow transplantation.*"	[10]
American Society of Hematology (ASH)	"*Further research is needed in hospitalized medical patients with cancer. More information is needed on the optimal choice, dosing, and duration of parenteral anticoagulation to prevent VTE for hospitalized patients with cancer. Further information is also needed on the dosing of anticoagulation for obese patients, underweight patients, patients with hematological malignancies or undergoing stem cell transplantation, and patients with renal disease.*"	[11]
National Comprehensive Cancer Network (NCCN)	No specific recommendations rendered.	[12]

For the patients who did experience VTE, Lee et al. report that the Khorana risk score was < 3 (low to intermediate risk) [1], and similar phenomenon to this was also noted in prior studies with hematologic malignancy patients: retrospectively calculated median SAVED scores in both D-RVd and RVd groups of GRIFFIN were in the low-risk VTE category (<2 points) [0 (range, 0–3) and 0.5 (range, 0–4), respectively], suggesting that despite low predicted risk, the observed incidence of VTE in both these groups was relatively high [8]. This raises a question of suitability of these risk-scoring tools in these settings, albeit final verdict is still not possible in the absence of prospective RCT data.

The study by Lee et al. crucially demonstrates the essential need for RCTs to address this gap in knowledge and supportive care practice for HSCT recipients - in a risk-stratified manner. While stronger argument can be made for autologous HSCT recipients, it remains unclear whether allogeneic HSCT patients belong to the group who may benefit from VTE prophylactic measures: in their subgroup analysis, Lee et al. demonstrated that allogeneic versus autologous HSCT patients had an increased risk of bleeding (OR 3.35, 95% CI, 1.79–6.25, $p = 0.0002$), despite decreased risk of VTE events (OR 0.69, 95% CI, 0.22–2.12, $p = 0.50$) [1].

Thromboembolism does not only interfere with safe and optimal oncologic care, but also represents a leading cause of death in cancer patients receiving chemotherapy [13]. Rates of VTE incidence in the modern times are demonstrably unacceptable in many hematologic malignancies, many of which are treated with standard of care HSCT therapy. As such, we echo the message of Lee et al. as well as national recommendation bodies towards larger, prospective and risk-adapted RCTs to confirm the safety and benefit of VTE prophylaxis, in both autologous and allogeneic HSCT recipients.

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COMPETING INTERESTS

MB—Consultancy: Cardinal Health, AbbVie. Advisory Boards: Janssen Biotech, Karyopharm, BMS/Celgene. Speaker: NCCN, Curio Science, Targeted Oncology. IRCs: Parexel. DWS—IRC: Paraxel. Advisory/consultancy: Pfizer, bioline, Janssen, BMS, Sanofi, A rcellx.

ADDITIONAL INFORMATION

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