

Late effects on haemostasis after haematopoietic stem cell transplantation

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Keywords

Haemostasis, venous thromboembolism, atherosclerosis, GvHD

Summary

Allogeneic and autologous hematopoietic stem cell transplantations are important therapeutic options for patients with hematologic disorders. Hemostatic complications are frequent after hematopoietic stem cell transplantation with a considerable morbidity and mortality. The incidence of bleedings and thrombosis is highest in the first few weeks after transplantation, but may also occur later. However, beyond the first year of transplantation only limited data are available. In long-term survivors the risk for premature atherosclerosis increases over time after allogeneic hematopoietic stem cell transplantation and it is higher than in the age-adjusted general population and in recipients of autologous transplantation.

Schlüsselwörter

Hämostase, venöse Thromboembolie, Atherosklerose, GvHD

Zusammenfassung

Die allogene und autologe hämatopoietische Stammzelltransplantation ist eine wichtige therapeutische Option für Patienten mit hämatologischen Erkrankungen. Komplikationen der Hämostase sind relativ häufig und verursachen eine beträchtliche Morbidität und Mortalität. Blutungen und Thrombosen treten am häufigsten in den ersten Wochen nach der Transplantation auf, es sind jedoch auch Fälle im späteren Verlauf der Transplantation beschrieben. Über hämostatische Komplikationen, die nach einem Jahr auftreten, existieren nur noch sehr wenige Daten. Bei Langzeit-Überlebenden Patienten nach allogener Stammzelltransplantation nimmt im Laufe der Zeit das Risiko für zerebro- und kardiovaskuläre Ereignisse deutlich zu. Das Risiko ist höher als in der Alters-adaptierten Allgemeinbevölkerung und in Patienten nach autologer Stammzelltransplantation.

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Venous thromboembolism (VTE) and bleeding disorders are common complications after HSCT with a cumulative incidence of approximately 5%. Most of the thromboembolic complications and bleeding events occur relatively early after HSCT (4–6). Beyond the first year after autologous and allogeneic HSCT, these complications are less frequent, but data are relatively sparse. With longer follow-up, however, the risk of arterial cardiovascular complications increases being clearly higher than in an age-adjusted normal population. Thus, awareness for cardiovascular long-term complications and the consequent treatment of risk factors has become increasingly important for physicians treating patients after allogeneic HSCT (7).

This review summarizes the current knowledge of haemostatic problems beyond the acute phase after allogeneic and autologous HSCT.

Late events after HSCT

Venous thromboembolism

Although venous thromboembolism may occur at any time, the risk is highest in the first few months after HSCT (6, 8). In the early posttransplant period the incidence and risk factors of VTE are well known. Among others, it is often associated with indwelling central venous catheters, acute GvHD, residual tumour load, and calcineurin inhibitors (8, 9). The largest study retrospectively analyzed the VTE incidence in 1514 HSCT recipients (928 autologous, 586 allogeneic) with a median follow-up of 642 days. The median time until VTE was 35 days after admission and 63 days until the occurrence of a non-catheter associated VTE. At day 180 the overall cumulative VTE incidence was 4.6% and the incidence

Haematopoietic stem cell transplantation (HSCT) is often the only curative option for malignant and non-malignant hematologic disorders. Advances in the transplantation techniques and the supportive care strategies have resulted in a significant improvement of the overall survival. Among those patients who survive more than two years, nearly 80% of allogeneic HCT recipients and 70% of autologous

HCT recipients will become long-term survivors (1). Therefore, an increasing number of patients after allogeneic HSCT are at risk of developing long-term complications (2, 3) including chronic GvHD, secondary malignancies, pulmonary complications, but also late venous and arterial thromboembolic complications and premature atherosclerosis.

of non-catheter associated VTE was 0.7%. Later events were not evaluated in this study. Importantly, no deaths were directly associated with VTE and only one patient had pulmonary embolism at autopsy, which was not believed to be the cause of death. In multivariate analysis, the most important risk factors were

- a previous thromboembolic event,
- acute GvHD, and
- the use of corticosteroids.

Other thromboembolic risk factors such as factor V Leiden and the prothrombin mutation have only a moderate influence of the posttransplant VTE incidence most likely due to the overwhelming effect of GvHD on VTE (10).

A second study analyzed the incidence of VTE in 589 patients (382 autologous, 207 allogeneic HSCT) within the first year after transplantation. The cumulative one-year incidence of VTE was 3.7%, whereas the incidence of non-catheter related VTE events was only 1.2%. In this study, the median time to the non-catheter related VTE was 153 (71–219) days after allogeneic HSCT and 312 (256–328) days after autologous HSCT.

The later time point of the thrombosis might be at least in the group of allogeneic recipients due to a prophylactic administration of low-molecular heparins. When comparing autologous with allogeneic HSCT, the overall incidence of VTE and the incidence of pulmonary embolism were more frequent in the later group, in particular in patients with GvHD.

Only very limited data are available regarding thromboembolic complications beyond the first year after HSCT. Few studies analyzing long-term survivors include late VTE events without providing more details (3, 11). Chronic GVHD has been associated with late thromboembolism. Endothelial stimulation in the context of GVHD or the presence of endothelial-derived microparticles, which induce a prothrombotic potential, might be associated co-factors. In long-term survivors, diagnosis and treatment of late thromboembolism follow standardized criteria as for patients without HSCT. The choice of anticoagulant (vitamin K antagonist or low-molecular-weight heparin) might depend

on the presence and severity of chronic GVHD, as well as on the patient's compliance (12).

Bleeding complications

Bleedings occur mostly early after HSCT in the context of cytopenias and mucositis, with a high rate of fatal bleedings (4, 6, 13). Late-onset bleedings are mostly described in patients receiving anticoagulation for thromboembolic complications, or with acute and chronic GvHD. Recently, it has also been suggested that sirolimus may cause bleedings after HSCT (14). In multivariate analysis, anticoagulation has been the strongest predictor of bleeding (6). In addition, several reports have looked organ-specific late-onset bleeding complications such as diffuse alveolar haemorrhage, haemorrhagic cystitis, and intracranial haemorrhages without giving detailed information on the incidence and time point of onset (14–16). Thus, bleeding complications are frequent early after HSCT, whereas the information about the incidence and clinical implication in long-term survivors is sparse.

Arterial thrombosis and premature atherosclerosis

Haematopoietic cell transplantation survivors are at risk for a variety of cardiac and cardiovascular complications due to the combined effect of

- pre- and post-HSCT therapies,
- conditioning regimens and
- acute and chronic GvHD.

For a long time, arterial thromboses have not been studied due to their extremely low frequency and their late-onset after HSCT. Only few case reports have described such cases and the incidence of this complication was not established (17). Recently, two large retrospective studies have elucidated the incidence of cardiovascular events in long-term survivors after allogeneic HSCT.

In a single-center analysis, Tichelli and colleagues retrospectively compared a cohort of allogeneic and autologous patients.

Allogeneic patients had an increased risk for cardiovascular events with a median time of appearance of 9 years after HSCT (range 2–21 years). In the years following HSCT, 6.8% of the patients presented with an arterial vascular event. The median age of the affected patients at the time of the event was 49 years. The cumulative incidence of a cardiovascular event in this cohort was 22.1% at 25 years.

This is markedly higher compared with a general male population without HSCT and with an intermediate risk profile, where the cumulative incidence is 11% at 50 years. Arterial complications consisted of cerebro- and cardiovascular and peripheral arterial events. These data show that atherosclerotic disease occurs significantly earlier than in an age-adjusted general population and is more frequent after allogeneic than autologous HSCT. Established risk factors, such as hypertension, diabetes and dyslipidaemia, were significantly associated with late arterial vascular events in a univariate analysis. Age, TBI and chronic GVHD did not show any association with vascular events in the same cohort.

These data were confirmed in a multi-center study under the auspices of the European Group for Blood and Marrow Transplantation (18). In this study, the cumulative incidence fifteen years after HSCT was 6% and the median age of onset 54 years. The cumulative incidence was clearly higher for patients with high cardiovascular risk score (17%) as compared to patients with low risk score (4%).

Risk factors for atherosclerotic disease are more common in patients after allogeneic HSCT. A large retrospective study has shown that diabetes, hypertension and dyslipidaemia are more common in long-term survivors after allogeneic HSCT (19). Concomitant medication (steroids, immunomodulators), gonadal dysfunction or premature endothelial damage in the context of GVHD are possible trigger events for this development. Thus, the recommended screening and preventive practices for long-term survivors also includes the regular control of cardiovascular risk factors (7).

Possible mechanisms of premature atherosclerosis

GvHD is a major cause of early and late morbidity and mortality after HSCT. Generally, the main targets of GvHD are epithelial structures as measured by the presence of cytokeratin fragments in the serum (20). However, several posttransplant complications are predominantly endothelial cell disorders, but related to GvHD, such as

- transplant-associated microangiopathy,
- veno-occlusive disease,
- haemorrhagic cystitis, and
- diffuse alveolar haemorrhage.

Hence, it has been hypothesized that these complications are caused by an endothelial form of GvHD (21, 22). There are several arguments in favour of this hypothesis (► Tab. 1). It has been demonstrated that GvHD leads to changes in a variety of endothelial markers such as thrombomodulin, plasminogen activator inhibitor, von Willebrand factor, endothelin, VEGF, or VCAM and ICAM (23–32).

Recently, it has been demonstrated that steroid-refractory acute GvHD causes a simultaneous reduction of thrombomodulin on the endothelial cells and a rise of soluble thrombomodulin in the plasma (27). Vascular endothelium dysfunction has also been demonstrated by circulating endothelial cells, endothelial microparticles, and by inducing apoptosis of the microvascular endothelial cells using plasma of patients with TAM (29, 33, 34). Lastly, several reports have established a clinical correlation between posttransplant microangiopathy and GvHD (35, 36).

Thus, there is a growing body of evidence that both acute and chronic GvHD is associated with inflammatory changes of the endothelium.

Atherosclerosis is now considered as an inflammatory process occurring years to decades before the clinical symptoms arise. Hence, it is conceivable that long-standing subclinical endothelial inflammation causes premature atherosclerosis in long-term survivors after allogeneic HSCT. In line with this, several reports have shown that chronic GvHD leads to morphological

Tab. 1

Endothelial activation markers associated with graft-versus-host disease

activation marker		ref.
endothelial cell markers	von Willebrand factor	23, 37
	plasminogen activator inhibitor-1	24, 26
	thrombomodulin	25, 27
	endothelin	28
	Fas/Fas-ligand	29
	VEGF	30
	VCAM/ICAM	31, 32
	E-selectin	31
structural changes	vessel rarefaction	37
	neovascularization	38
	endothelial apoptosis	39
	endothelial microparticles	29
	circulating endothelial cells	33, 34

changes of the vasculature. Biedermann et al. have demonstrated that chronic GvHD is associated with a rarefaction of vessels in skin biopsies, while others have found neovascularization during and after GvHD (37, 38).

Conclusion

The most important late haemostatic complication are premature atherosclerosis and arterial vascular events. These events generally occur many years after allogeneic HSCT. Pathogenetically, endothelial damage due to acute and chronic GvHD is associated with a variety of vascular complications after allogeneic HSCT. Most probably, long-standing – potentially subclinical – chronic GvHD affecting the endothelium contributes to premature atherosclerosis.

Physicians treating patients after allogeneic HSCT should be aware of this complication and rigorously monitor and treat risk factors for cardiovascular disorders.

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