SCIENTIFIC PAPER

Hepatitis B infection in haematopoietic stem cell transplantation: still unresolved

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Impact of hepatitis B virus (HBV) infection on haematopoietic stem cell transplantation (HSCT) was reported earlier since late 1980s. It was shown that changing patterns of HBV serological markers was accompanied by variable severity of hepatitis after transplantation. Recipient's hepatitis B virus surface antigen (HBsAg) positivity was not considered an absolute contra-indication to allogeneic HSCT. However, HBsAg positivity was an important risk factor of reactivation hepatitis after transplantation, especially in allogeneic setting. Managing HBV reactivation in HSCT recipients was not successful till the availability of lamivudine since mid-1990s. For HBsAg-positive recipients, prophylactic lamivudine has been shown to significantly reduce reactivation hepatitis. As for HBsAg-negative recipients, there have been a small number of patients who develop so-called reverse seroconversion, that is, appearance of HBsAg after transplantation. In addition to chronic graft-versus-host disease, the risk was also high in allogeneic HSCT recipients who received fludarabine–antithymocyte globulin–containing conditioning regimens. The HBV is harboured earlier in the recipients before transplantation rather than transmitted via transfusion. At present, the optimal duration of lamivudine prophylaxis is not well-defined, and there are several fatal cases associated with early withdrawal and resistant HBV mutants. In conclusion, in HBV-endemic areas, the war between HBV and HSCT recipients continued even though several anti-HBV agents and molecular detection techniques are available. It deserves additional effort to overcome and also presents a chance to elucidate underlying mechanisms of HBV immunity, which are not easily studied in non-HSCT setting.

Introduction

Hepatitis B virus (HBV) infection has been a worldwide health problem, with two billion people having been infected with HBV, 360 million chronic carriers of HBV surface antigen (HBsAg), and 600 000 annual deaths from HBV-related liver disease or hepatocellular carcinoma.[1] Three quarters of chronic carriers are Asians. In Taiwan, about 15% of adult patients receiving haematopoietic stem cell transplantation (HSCT recipients) are positive to HBsAg prior to transplantation.[2] HBV-associated events have significantly complicated post-transplant courses of HSCT recipients in Taiwan and in other Asian areas. In this article, the progress regarding HBV infection in HSCT will be summarised, focusing on several important findings from this endemic area.

Key words
Hematopoietic stem cell transplantation; Hepatitis B virus; Lamivudine; Virus activation

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Problem learning

As earlier studies in 1980s found HBV reactivated in patients receiving immunosuppressive therapy and chemotherapy,[3,4] HSCT were once considered a contra-indication in HBsAg-positive patients in western countries. However, it was unavoidable in Asia. Following clinical application of HSCT in Taiwan in 1983, Chen et al[5] (Taipei Veterans General Hospital) first reported the complexity of HBV infection after HSCT, and demonstrated that there were changing patterns of HBV serological markers, accompanied with variable severity of acute and chronic hepatitis, after transplantation. In a cohort of 42 patients with a follow-up of 3 to 12 months after transplantation, they found that 12 (44%) out of 27 had altered HBV serological markers, including seroconversion of HBsAg, clearance of anti-HBs antibody, appearance of HBV e antigen, clearance of anti-HBe antibody, and acute hepatitis. One patient died of fulminant hepatitis.[5] Thereafter, many studies regarding HBV infection in HSCT have investigated different recipient population and transplant modalities.[6] On the other hand, the finding that HBV infection only contributed a relatively low mortality following transplantation provided the evidence that recipient's HBsAg positivity should not be a contra-indication to allogeneic marrow transplantation.[7] Although there are increasing rates of reactivation and fatal hepatitis after transplantation, most of the studies did not support a direct relationship of HBV status and overall survival of HBCT recipients.[5,8-11] In a long-term follow-up study, Hui et al[12] found that the incidence of liver cirrhosis in HBsAg-positive HSCT recipient can actually be reduced if they sustained

serologic clearance of HBsAg after transplantation.

Identification of risk factors and intervention

There were many studies to identify risk factors associated with HBV reactivation after transplantation and after chemotherapy. In general, HBsAg positivity of both recipients and donors is important and has been used to select the population of intervention therapy.[5,8-11] In allogeneic setting, HBV replicates rapidly following transplantation and manifests with clinical hepatitis following immunosuppressant withdrawal, especially preceding and/or concomitant with development of graft-versus-host disease (GVHD).[13] In autologous setting, HBsAg-positive patients with detectable serum HBV DNA before HSCT (on Digene assay: 1.42 x 10^5 copies/mL) had a significantly higher risk of hepatitis due to HBV reactivation.[14] As for HBV variant and genotype, their impact in HSCT setting was controversial.[14,15]

Earlier intervention to prevent HBV reactivation and rescue HBV hepatitis following HSCT was usually not successful till the availability of lamivudine—a negative enantiomer of 3-thiacytidine. Along with several cases reported, Lau et al[16] first showed that 1-year use of prophylactic lamivudine in allogeneic HSCT recipients significantly reduced reactivation hepatitis. Later, we further showed the efficacy of extended lamivudine (median, 73 weeks) in reducing the incidence of reactivation hepatitis in a cohort of 71 HBsAg-positive HSCT patients.[11] Both studies showed the efficacy of primary prophylaxis or pre-emptive lamivudine in reducing the incidence of reactivation hepatitis in HBsAg-positive HSCT recipients. At present, these findings have been adopted to a routine prophylactic policy in HBsAg-positive HSCT recipients worldwide to prevent HBV reactivation after transplantation.

Reverse seroconversion

There has been a small number of HBsAg-negative HSCT recipients who develop so-called reverse seroconversion, ie appearance of HBsAg after transplantation.[5,17] Although Seth et al[18] showed such development associated with chronic GVHD, the phenomenon has not been well investigated in the HBV-endemic area. However, following the application of reduced-intensity conditioning (RIC) in patients with older ages, we found that reverse seroconversion risk was highest in allogeneic HSCT recipients who received fludarabine-antithymocyte globulin–contained RIC regimens. Subsequent works further demonstrated the origin of HBV in selected cases is indeed derived from the recipients themselves before transplantation rather than from transfusion (submitting). In HBV-endemic areas, the finding would provide a rationale to select a more suitable population of HBsAg-negative HSCT recipients to receive HBV monitoring and prophylaxis.

B型肝炎病毒對造血幹細胞移植病患影響：尚未完全克服

B型肝炎病毒感染對造血幹細胞移植影響的研究主要從80年代末起，陳氏等首先報告移植後部份病患發生B肝血清學標記改變，甚至合併急性B肝發炎及死亡情形。此報告及後續研究證明：B型肝炎病毒感染對造血幹細胞移植病患的整體存活影響有限，推翻了「B型肝炎病毒感染的病患是造血幹細胞移植禁忌」的論點。而最重要的移植後B肝發作危險族群是表面抗原帶原的病患，尤其是異體移植後。處理移植後B肝發作的努力一直到抗病毒藥物lamivudine的上市才算成功，目前已證明在表面抗原帶原的造血幹細胞移植病患身上，可有效減少移植後B肝發作情形。至於B肝表面抗原陰性的病患在移植後偶有血清反逆轉情形，亦即「表面抗原的抗體消失，抗原出現」，先前報告指出併有慢性移植物對宿主反應的病患好發，最近我們發現：在使用含fludarabine-抗T細胞球蛋白移植處方的病患也有明顯增加發生情形，同時確認「在反逆轉時，B肝病毒是早已於移植前即存在病患體內」。目前仍待釐清的課題，包括lamivudine的使用時間，因已有案例發生因停藥後復發或抗藥菌株出現導致的死亡。因此，雖然抗病毒藥物及檢測方法已大幅進步，但在B肝流行區的我們，其造血幹細胞移植病患的影響仍有許多課題值得克服及深入探討。

Unresolved problems

Optimal duration of anti-viral prophylaxis

The optimal duration of antiviral prophylaxis in HSCT recipients is not well defined. Such prophylaxis is complicated by concomitant development of transplant-related events and/or re-treatment of relapsed diseases after transplantation. It would be inappropriate to extrapolate from HBV studies in patients only receiving chemotherapy.[19] Fatal HBV recurrence after withdrawal of prophylactic lamivudine has been reported in several cases of chemotherapy and HSCT recipients.[20-22] On the other hand, prolonged lamivudine therapy is associated with an increased likelihood of developing resistant mutants. We recently found several HBsAg-positive HSCT recipients who received early prophylactic lamivudine since the initiation of induction chemotherapy, and rapidly developed fatal mutant-HBV reactivation (unpublished). Hence, the success of lamivudine prophylaxis in HBsAg-positive HSCT recipients may paradoxically contribute to the development of fulminant hepatitis associated with early drug withdrawal and resistant HBV mutant associated with extended drug use.

Vaccination and donor-directed policy

As described above, most adult HBsAg-negative recipients of HBV endemic areas have been exposed to HBV earlier, ie positive to antibody for

HBV core antigen (anti-HBc Ab). They have risks of reverse seroconversion after transplantation. Timely vaccination along with pre-emptive antiviral therapy may be useful to prevent it, but the optimal schedule in the HBV endemic areas is not well-studied. On the other hand, several reports demonstrated the efficacy of donor-directed measures, including anti-viral therapy prior to transplantation to decrease viral loads of HBsAg-positive donors, and/or enhancing the HBV-immune response of HBV-naïve donors for HSCT adoptive transfer.[23-25] Similarly, there is no standard schedule at present.

Conclusion

In HBV-endemic areas, the war between HBV and HSCT recipients continued despite the availability of potent anti-viral agents and molecular detection techniques. Previous works have resolved several important HBV-related problems in HSCT recipients, especially for those positive to HBsAg. However, several issues remain to be clarified, and deserve additional effort to overcome the clinical challenge and also to elucidate underlying pathophysiological mechanisms.

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