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Recommendations for VZV management in patients with leukemia

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ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Immunocompromised Host Society

Introduction

- Acute VZV infection causes varicella (chickenpox), a common childhood disease, and reactivation of a latent infection in VZV seropositive patients causes zoster.

- Leukemia patients and SCT recipients are at risk for visceral dissemination of VZV infection (e.g., meningitis, pneumonitis, hepatitis), with or without skin manifestations, which may be fatal.

Introduction

- Leukemia patients and SCT recipients are at risk to develop varicella, which can be very severe and even fatal, after exposure to a patient with VZV. Steroids treatment increases the risk of severe varicella. The risk is considered highest <24 months after SCT, or beyond 24 months if on immunosuppressive therapy and/or having chronic GVHD.

- Studies of SCT recipients proved that acyclovir, in addition to promoting faster disease resolution, is highly effective at preventing VZV dissemination.

Introduction

- Although the risk to develop varicella after exposure is mainly in previously VZV seronegative HCT recipients, patients who were seropositive before SCT can become seronegative and therefore vulnerable to a second 'primary' infection with a clinical picture of chickenpox. This is especially true for those who are seropositive following receiving the varicella vaccine, as the vaccine is only partially protective.

- Healthy individuals who are immunized with the live attenuated VZV vaccine may transmit the virus to others, especially if they develop a rash. Such rash may occur between 5 and 35 days after vaccination (median 22 days).

Introduction

- Most of the SCT recipients nowadays are VZV seropositive, following varicella in their childhood or following immunization with live attenuated vaccine.

- VZV seropositive allogeneic and autologous SCT recipients carry a 20–50% risk of developing a zoster, usually occurring 3 to 12 months (median 5 months) post SCT. Patients with an HLA mismatched donor and under GvHD treatment have a higher risk; this also applies to infectious sequelae later on.

Introduction

- The incubation period of VZV is 10-21 days after contact.
- It may be prolonged for as long as 28 days after receipt of VZV immune globulin or IVIG.

- VZV disease that occurred after one year acyclovir prophylaxis usually responds well to treatment, suggesting that drug resistance is not a major problem.

Introduction

- VZV transmission by marrow or stem cell products has not been documented.

- There is no data with regards to the benefit, as well as the minimum interval required between immunization and transplantation, about immunization of VZV seronegative leukemic patients in remission who are candidates for SCT with the live attenuated varicella vaccine prior to the SCT.

Diagnostic tests for VZV infection

Test	Specimen	Comments
Viral culture	Vesicular fluid, CSF, biopsy tissue	VZV is detected from only 60%–75% of specimens; limited availability, cost, requires 1-2 weeks
PCR	Vesicular swabs or scrapings; scabs from crusted lesions; biopsy tissue, CSF	Very specific and sensitive. Real-time PCR can distinguish vaccine strain from wild-type. Expensive
DFA	Vesicle scraping; swab of lesion base (must include cells)	specificity - 95%. sensitivity - 90%. rapid-3h
Tzanck smear (observe multinucleated giant cells with inclusions)	Vesicle scrapping: swab of lesion base (must include cells)	Not specific for VZV. Less sensitive and accurate than DFA

How to minimize the risk of leukemic patients and SCT recipients from being exposed to a patient with varicella

- Leukemic patients and SCT candidates and recipients should be informed about VZV transmission and advised of strategies on how to avoid exposure (AIII).

- Vaccination of family members, household contacts and health care workers, known seronegative for VZV or children with no history of VZV infection should be performed (BIII). The vaccination of the seronegative individuals who may be in contact with the patient is to be performed >4 weeks prior to start of conditioning (BIII).

How to minimize the risk of leukemic patients and SCT recipients from being exposed to a patient with varicella

- VZV seronegative leukemic patients and SCT recipients should avoid exposure to people with chickenpox or zoster (AII). The risk for VZV seropositive patients is low.

- Leukemic patients, before and after SCT, should also avoid vaccine recipients who experience a rash after vaccination (BIII).

How to minimize the risk of leukemic patients and SCT recipients from being exposed to a patient with varicella

- All patients with varicella or disseminated zoster should be placed under airborne and contact isolation. The isolation should be continued as long as the rash remains vesicular (BIII).

- In VZV seronegative patients, long-term acyclovir prophylaxis for 6 months (or longer in severe GvHD) to prevent varicella is not recommended (DIII).

Management of VZV seronegative leukemic patient and SCT recipient after exposure to varicella or zoster

Types of exposure which necessitate intervention:

- Household: residing in the same household
- Playmate: face to face (a contact of 5 minutes or more) indoor play
- Hospital: In same room or adjacent beds in a large ward, face to face (a contact of 5 minutes or more) with a person deemed contagious with varicella or with immunocompromised host with disseminated zoster, or intimate contact (touching or hugging) with a person with zoster.

Management of leukemic patient and SCT recipient after exposure to varicella or zoster

- Passive immunization with i.v. VZV hyperimmune globulin (at a dose of 0.2-1 ml/kg) or i.m. VZV immune globulin (VZIG), or IVIG, should be given as soon as possible after exposure (<96 hours) to VZV seronegative leukemic patients on chemotherapy and those receiving steroids (up to 4 weeks after steroids were discontinued), and to VZV seronegative SCT recipients patients who have chronic GvHD, are on immunosuppressive treatment, or whose SCT dates back <2 years (AII).

Management of leukemic patient and SCT recipient after exposure to varicella or zoster

- In case that passive immunization was not administered, post-exposure prophylaxis with acyclovir or valacyclovir is recommended (AIII). If the exposure was known later, the prophylaxis should be started up to day 22 after the exposure (BIII).

- If a second exposure occurs more than 21 days after a dose of passive immunization in a susceptible individual, a prophylaxis should be re-administered (BII).

Management of leukemic patient and SCT recipient after exposure to varicella or zoster

- Seronegative leukemic patients or SCT recipients should also receive prophylaxis if they are exposed to a VZV vaccinee having a varicella-like rash (BIII).

- In VZV seronegative, potentially contagious patients, airborne precautions should be instituted 10 days and continued until 21 days after the last exposure or 28 days post-exposure if the patient received varicella-zoster passive immunization (AIII).

- Prophylaxis in VZV seropositive patients is optional (CIII).

How to prevent zoster after SCT

- Determination of VZV IgG serostatus is recommended in all SCT candidates (AIII).

- Prophylaxis with oral acyclovir (800mgx2 daily) or valacyclovir (500 mg 1-2 daily) is recommended for seropositive allogeneic SCT recipients, for one year (AII), or longer in the presence of GVHD and immunosuppressive therapy (BII)

- Prophylaxis for autologous SCT is controversial.

The live attenuated VZV vaccine for leukemic children

- Although the current live attenuated vaccine is not licensed for routine use in children with malignant neoplasms, immunization should be considered when a susceptible child with ALL has been in continuous remission for at least 1 year and has lymphocyte counts greater than 700/uL ($0.7x10^9$/L) and platelet counts greater than $100x10^9$/L (BIII).

The live attenuated VZV vaccine for SCT recipients

- There is no data with regards to the benefit, as well as the minimum interval required between immunization and transplantation, about immunization of VZV seronegative leukemic patients in remission who are candidates for SCT with the live attenuated varicella vaccine prior to the SCT.

The live attenuated VZV vaccine for SCT recipients

- If there is no chronic GVHD or ongoing immunosuppression, vaccination of VZV seronegative SCT recipients can be considered at 2 years after SCT (CIII).

- VZV vaccine use is contraindicated for routine use in individuals <24 months after SCT, and later on in those with GVHD and immunosuppressive therapy (EIII).

Treatment

- Patients treated for leukemia and SCT recipients who experience a VZV-like rash should be started immediately on i.v. acyclovir 500 mg/m^2 every 8 hours until 2 days after all lesions are crusted (AI).

- High suspicion of visceral VZV disease without mucocutaneous manifestations (e.g., in cases of encephalitis, pneumonitis or hepatitis) is needed, and intravenous acyclovir 500 mg/m^2 every 8 hours should be considered in such cases (AIII).

Treatment

- Oral valacyclovir (3x1000mg, famciclovir 3x500mg, acyclovir 5x800mg, or brivudine 125 mg once daily) are alternative options for recipients with stable localized disease (CII).
- Brivudine is absolutely contraindicated in patients receiving 5-fluoropyrimidines derivates (EII).

- A rash following exposure to a VZV vaccine should be treated similarly (BIII).

- Foscarnet or cidofovir are alternatives anti-VZV treatment in a case of acyclovir resistant varicella or zoster (BIII).

Optional oral therapy for controlled VZV infections

Medication	Dosage; duration	Pediatric dosage	Cautions in
Acyclovir	800 mg 5 times daily; for 7–10 days	20 mg/kg 4 times a day	renal insufficiency
Valacyclovir	1000 mg 3 times daily; for 7 days		renal insufficiency; TTP and HUS reported
Famciclovir	250-500 mg 3 times daily; for 7 days		renal insufficiency
Brivudine	125 mg once daily; for 7 days	5 mg/kg/d in 3 divided doses	Absolute contraindication in patients treated with 5-fluorouracil or other 5-fluoropyrimidines