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BRIEF REPORT

Immunogenicity and Safety of Yellow Fever Vaccine in Allogeneic Hematopoietic Stem Cell Transplant Recipients After Withdrawal of Immunosuppressive Therapy

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As a live attenuated vaccine, yellow fever vaccine (YFV) is not routinely performed after allogeneic hematopoietic stem cell transplant (HSCT) despite it being the only efficient preventive therapy. We retrospectively identified 21 HSCT recipients immunized with YFV at a median of 39 months after HSCT and a median of 33 months after withdrawal of immunosuppression without any side effects. Eighteen evaluable patients had protective immunity after YFV. We also observed that a third of the recipients vaccinated with YFV before HSCT had persistent protective immunity after HSCT.

Keywords. yellow fever; live attenuated vaccine; allogeneic transplantation; immunocompromised.

Immunization is the only efficient preventive therapy for yellow fever (YF), a life-threatening viral hemorrhagic fever transmitted by mosquitos in Africa and South America. Yellow fever vaccine (YFV) produces a high level of protection, with seroconversion rates exceeding 95% within 30 days and lasting over 10 years. YFV is a life-attenuated vaccine, contraindicated in immunocompromised patients. However, immunization has been performed safely in human immunodeficiency virus (HIV)–infected patients with a CD4 count >0.2 × 10^9 cells/L [1]. To date, only 2 patients immunized with YFV after allogeneic hematopoietic stem cell transplantation (HSCT) have been reported in the literature [2, 3]. Although vaccine guidelines allow YFV in HSCT recipients free of graft-vs-host disease (GVHD) and of immunosuppressive drugs beyond 2 years posttransplantation, most physicians are reluctant to perform YFV and usually provide medical exemption to vaccination to HSCT recipients or recommend limiting travels to countries at risk [4]. This attitude is probably due to the lack of published data on YFV after allogeneic HSCT, contrasting with measles, mumps, and rubella (MMR) vaccines—other life-attenuated vaccines—for which prospective studies in HSCT recipients were published in the 1990s. To evaluate the safety and immunogenicity of the YFV in HSCT recipients, we performed a retrospective analysis in 2 transplant units and 2 travel clinics (Saint-Louis Hospital and Institut Pasteur Medical Center).

MATERIALS AND METHODS

Patients were retrospectively identified from 6 transplant units in France from 2007 to 2015. Clinical and medical data were collected through patient and transplant physician interviews. YF immunization was performed with the YF-17D204, currently the only vaccine licensed in France (Stamaril, Sanofi-Pasteur, Lyon, France). Serological analyses were performed at Laboratoire Cerba, using the plaque reduction neutralization test, which is a standard technique for assessing humoral response to YF-17D immunization. The YF antibody titers are expressed as the reciprocal of the last serum dilution to show 80% reduction of the plaque control. A YF virus neutralization test (YF-NT) of 10 U/L is accepted as a marker for clinical protection [5]. Eighty units per liter is the highest value. Continuous variables are presented as median, interquartile range (IQR), and range. All patients gave their consent for publication of the data. Of note, some patients had not informed the vaccination centers of their transplant history.

RESULTS

Twenty-one allogeneic HSCT recipients immunized with YFV after HSCT were identified. Patients, HSCT, and posttransplant characteristics are detailed in Table 1. None had active GVHD, and all patients but 1 were free of immunosuppression at the time of vaccination. One patient had 2 mg/day of prednisolone. YFV was performed at a median of 39 months after HSCT (range, 12–270 months; IQR, 21–86 months) and a median of 33 months (range, 5–246 months; IQR, 10–72 months) after withdrawal of immunosuppression. The median lymphocyte count at time of YFV was 2.3 × 10^9 cells/L (IQR, 2–3; n = 21) and the CD4 T-cell count was 0.72 × 10^9 cells/L (IQR, 0.60–0.80; data available in 17 patients). Gamma-globulin levels were normal in the 14 evaluable

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Table 1. Patient, Disease, and Hematopoietic Stem Cell Transplantation Characteristics and Yellow Fever Vaccination History

Characteristic	No.
No. of vaccinated recipients	21
Diagnosis before HSCT	
Sickle cell disease	14
Aplastic anemia	1
Hematologic malignancies	
AML	4
CML	1
CLL	1
Age at HSCT, y, median [IQR] (range)	9 [5.5–17.9] (3–56)
Donor	
Related	19
Unrelated	2
Stem cell source	
Bone marrow	18
Peripheral blood stem cell	1
Cord blood	2
Conditioning regimen	
Myeloablative	20
Reduced intensity	1
Antithymocyte globulins (Thymoglobulin)	14
Dosage, mg/kg, median [IQR] (range)	20 [20–20] (12.5–20)
Graft-vs-host disease	
Acute GVHD (grade II only)	2 (9.5%)
Chronic GVHD	5 (24%)
Extensive chronic GVHD	2 (9.5%)
Yellow fever vaccination	
Age at YFV, y, median [IQR] (range)	15.1 [9.8–32] (5.1–61)
Time from HSCT to YFV, mo, median [IQR] (range)	39 [21–86] (12–270)
Time from last immunosuppressive drug to YFV, mo, median [IQR] (range)	33 [10–72] (5–246)
YF-NT value before YFV (n = 5 vaccinated before HSCT), IU/L, median [IQR] (range)	0 [0–0] (0–10)
Time from YFV to YF-NT, mo, median [IQR] (range)	30 [5–67] (1–120)
YF-NT value after YFV (n = 18), IU/L, median [IQR] (range)	80 [40–80] (10–80)
Follow-up after YFV, mo, median [IQR] (range)	20 [9.2–72.4] (4–124)

Abbreviations: AML, acute myeloblastic leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; GVHD, graft-vs-host disease; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; YF-NT, yellow fever neutralizing test; YFV, yellow fever vaccine.

patients. Of the 21 vaccinated patients, 8 had been immunized before transplantation; 5 were evaluated for YF antibody titer before post-HSCT immunization, and only 1 patient had a low protective titer (YF-NT = 10 U/L). Among the 21 patients vaccinated after HSCT, 18 were evaluated for immunogenicity; all had protective YF-NT titers at a median of 30 months after YFV (median YF-NT, 80 U/L [IQR, 40–80 U/L]). Disease, donor, source of stem cell, conditioning regimen, and posttransplant history had no impact on the level of YF-NT titers. In 5 patients, persistence of a protective level >5 years after YFV was observed (6–10 years). No side effects were reported in this cohort.

One patient immunized for YFV before HSCT had persistent immunity after transplantation with a vaccinated donor. As both donor and recipient had been immunized before HSCT, it was not possible to draw conclusions on the origin of the persistent protective immunity after HSCT.

To better understand the frequency and the origin of persistent protective immunity, we identified 12 additional cases where either the donor or recipient had been immunized prior to HSCT, and with known recipient post-HSCT serological status. These 12 recipients were not immunized after HSCT, but their serological status was evaluated after HSCT. Altogether, the immunized status after HSCT was studied for 17 recipients and analyzed according to the type of donor.

Altogether, we identified 7 pairs of donors/recipients both immunized before transplant: 5 recipients had persistent protective immunity after transplant (YF-NT = 10–80 IU/L at a median of 8.6 years post-HSCT), whereas 2 did not (YF-NT = 0 IU/L at a median of 3.9 years post-HSCT); GVHD did not have an impact on the serologic status after transplant. Conversely, in 7 recipients vaccinated before HSCT and transplanted with related nonimmunized or unrelated donor, immunity was lost (YF-NT = 0 IU/L at a median of 1.5 years post-HSCT). One adult patient immunized before HSCT had persistent immunity 2 years after an unrelated cord blood HSCT for refractory aplastic anemia (YF-NT = 80 IU/L). Finally, 2 patients who had not been immunized before HSCT and transplanted with an immunized related donor did not acquire protective YF titers after HSCT. Overall, all patients but 1 with persistent immunity after HSCT were transplanted with an immunized related donor.

Discussion

We report the largest cohort of HSCT recipients immunized with YFV. Our data support the safety of YFV after HSCT when performed in the absence of active GVHD and after withdrawal of immunosuppression. To date, only 2 adult allogeneic recipients immunized with YFV 3 and 10 years after HSCT were reported in the literature [2, 3].

The number of travelers in endemic areas is increasing yearly, including HSCT recipients [6], and YF outbreaks have been reported from 2015 in Africa and South America. YF-17D is highly efficient, but it is recognized as potentially harmful. Two very rare but severe diseases are related to the YFV: YFV-associated viscerotropic disease (YEL-AVD) and YFV-associated neurological disease (YEL-AND). A history of thymic disease has been reported in 4 of the 26 known fatal cases of YEL-AVD. Age >60 is also an important risk factor for YEL-AVD. In immunocompromised patients, only 1 case of fatal YEL-AND has been reported in an untreated HIV patient [7]. A large number of patients with HIV infection have been vaccinated safely and reported in the literature [8]. Nineteen patients with solid organ transplantation vaccinated with YFV have been reported without any side effects [9]. No side effects of the YFV were reported in our 21 patients. We cannot exclude formally unreported cases of severe side effects after YFV in HSCT recipients, but severe and unexplained complications

after vaccination in a HSCT recipient are usually reported to the referring physician(s).

Among the 21 patients vaccinated after HSCT, 8 had been vaccinated before transplant: In 4 of 5 evaluable patients, YF-NT was below the protective level before YFV and increased to protective levels after vaccination. Thirteen patients had their first YFV after HSCT and all 12 evaluable patients had protective immunity after YVF. Protective immunity was also evaluated in 5 of the 21 patients vaccinated after HSCT >5 years after YFV, all of whom had protective titers. Five patients received YFV before the 24 months usually recommended after HSCT. All patients but 1 were free of immunosuppression and, in all evaluable patients, CD4 lymphocyte counts and immunoglobulin levels were in the normal range at the time of vaccination.

Strikingly, we identified persistent YFV immunity in 6 of 15 patients vaccinated before HSCT. In the patient transplanted with an unrelated cord blood (presumably neither exposed to YFV nor YF), protective immunity was considered to originate from the sole recipient. In other cases, persistent protective immunity was strongly associated with a vaccinated related donor, but not with disease, history of GVHD, or time from HSCT. However, due to differences between related and unrelated HSCT procedures, heterogeneity of diseases, patients, and transplant histories, it is not possible to conclude that protective immunity originated from the donors in these patients. Moreover, in 2 additional pairs where only the donor was vaccinated before HSCT, a transfer of protective immunity was not observed. Persistent antibodies against MMR live attenuated vaccines were similarly observed in 30%–44% of the children tested at 1 year after HSCT before immunization [10].

The retrospective nature of this study inevitably leads to several limitations: (1) some cases may not be recorded; (2) no systematic evaluation of donor and recipient serological status for YFV before HSCT and after transplantation in the recipient was performed; and (3) in our cohort, the proportion of patients transplanted for sickle cell anemia is abnormally high compared to malignancies, but it reflects the needs for YFV that are particularly important in those patients mostly of African ancestry. Furthermore, there was no difference in tolerance and vaccine response between the subgroups of patients transplanted for malignancies or benign diseases.

A number of HSCT recipients may be tempted to travel to YF areas using pre-HSCT vaccination certificate. Our data demonstrate that most of them are not protected. Hematologists need to inform their patients that YFV performed before allogeneic HSCT may be invalid and that a consultation is necessary before traveling in endemic areas.

Conclusions

Yellow fever vaccination appears to be safe and efficient in allogeneic HSCT recipients free of GVHD and after withdrawal of immunosuppression. Immunization with YFV may be proposed to these patients after verifying immune recovery and beyond 2 years post-HSCT. Transfer of YF immunity from donor to recipient might be possible, although we were not able to demonstrate it in this study. Consequently, when a history of YFV is known in donor or recipient, YF antibody titers should be evaluated in recipients before performing new YFV. Prospective evaluation of YF antibody titers after HSCT in recipients transplanted with immunized and nonimmunized donors will help to understand the origin of the persistent protective immunity in some recipients.

Notes

Author contributions. All of the authors made substantial contributions to the conception of the study, the analysis and interpretation of the data, the drafting of the manuscript, and final approval of this manuscript.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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