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CORRESPONDENCE

DENGUE TRANSMISSION BY GRAFT OR BLOOD TRANSFUSION IN HCT RECIPIENTS

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Dear Sir,

Dengue is an arbovirus caused by a small RNA virus (DENV) belonging to the genus Flavivirus, family Flaviviridae, mainly transmitted by mosquitoes of the genus *Aedes*. However, dengue can also be transmitted by blood transfusion, blood components, or by the graft in solid organ (SOT) and hematopoietic cell transplantation (HCT).

Concern about non-vector transmission of dengue started in 2002, when the first cases of transfusion-transmitted (TT) dengue were reported in Hong Kong[1,2].

The current dengue epidemic in Brazil shows figures never before documented. By the end of March 2024, more than 2,300,000 probable cases of dengue had been registered, almost five times more than the number of cases reported during the entire year of 2023[3].

It is well known that dengue may present with a large percentage of asymptomatic cases (around 50%). Given the high activity of the current epidemic, HCT centers are rightly concerned about the likelihood of graft- or TT dengue, and the need for universal screening of donors.

Data from studies carried out in Brazil and around the world can help us evaluate the problem, answering the questions that naturally arise in the current situation:

1. What is the chance of an asymptomatic blood or hematopoietic cell donor having dengue viremia at the time of donation?

In blood donors from endemic countries, studies have documented viremia rates ranging from 0.04% to 0.8% during epidemics[4,5].

There are no studies on the rate of dengue viremia in HCT donors. However, it is reasonable to assume that such rates are similar to those for blood bank donors during epidemics.

2. Do all viremic donors transmit dengue to recipients?

No. A study carried out in Brazil by Sabino et al. demonstrated that approximately 1/3 of blood donations with positive PCR transmitted dengue during the DENV-4 epidemic in Brazil in 2012. The rate of TT dengue in that study was 37%. However, there was no difference in clinical symptoms or overall survival in recipients who received RNA-positive or RNA-negative transfusions. The lack of clinical impact of TT dengue observed in this study supported

the decision not to introduce dengue screening in blood banks in the country[5].

During epidemics, vector-borne dengue is by far the most common way to contract dengue. According to some authors, the lower infection rate observed after exposure to a human-derived parenteral inoculum compared to a mosquito-derived cutaneous inoculum can be explained by differences in glycosylation patterns of the virus replicating in mosquitoes or humans, and/or to the injection of mosquito saliva, which triggers local inflammation and other potentiating factors that can increase local viral replication and systemic infection[6,7].

Regarding HCT recipients, in a prospective cohort study carried out at the HCT Program of Hospital das Clínicas at USP, the authors observed that 5.3% of the 93 recipients had a serological diagnosis of dengue during follow-up (one by IgM detection and four by IgG seroconversion). None of the blood components infused into these patients showed a positive PCR for dengue. Therefore, no cases of TT dengue were recorded, and dengue cases were acquired through vector bites[8].

3) Are there cases of graft-transmitted dengue reported in HCT recipients?

To date, only 2 proven cases of dengue acquired by the graft have been reported in HCT. The first case occurred in a 6-year-old child during an epidemic of DENV 4 in Puerto Rico. The donor developed fever and headache the day following HCT. DENV 4 was retrospectively diagnosed in the donor by IgM detection. The recipient died of severe dengue 11 days after HCT[9].

The other case of DENV 1 was reported in Germany, in a 51-year-old HCT recipient, whose donor reported a recent travel to Sri Lanka, returning 3 days before the start of G-CSF mobilization. In the second day of apheresis, donor platelet count dropped to 47,000/mL and dengue was diagnosed by IgM, NS1 and PCR positive. Due to urgent medical need, HCT proceeded. Venoocclusive disease and dengue were diagnosed 3 days after HCT. Other bacterial and fungal infections followed and the patient died 9 days after transplantation[10].

In both cases, the viruses identified in the donor and recipient were genetically related.

Considering the Brazilian scenario of endemic dengue alternating with periods of epidemic, one would expect more reports of dengue in HCT recipients, if transmission through the graft were frequent and led to exuberant and severe clinical manifestations.

4) Is dengue transmitted by blood or transplant more severe than transmitted by mosquitoes?

Due to the lack of prospective studies on the incidence of dengue in HCT, it is not possible to estimate the real morbidity and mortality of dengue in this population.

The two published cases of graft-transmitted dengue died on d+11 and d+9 after HCT. In the case of the patient from Germany, it was not possible to assess the role of dengue in the patient's death due to concomitant severe venoocclusive disease and other complications[9,10].

Reviewing the literature, it is observed that the mortality rate attributed to dengue is higher in case reports compared to case series, both in SOT and HCT[11-14]. In general, reports of severe cases are published more frequently than those of mild or moderate cases, leading to publication bias and the false impression of high mortality. Indeed, a recent review of endemic and geographically limited infections, including published Brazilian cases of post-HCT dengue, showed that the vast majority of patients showed complete clinical recovery[15].

5) What are the immediate implications of implementing universal donor screening?

Firstly, the logistics of implementing and ensuring access to dengue diagnosis by PCR to all HCT centers. Once the diagnosis has been implemented, it is important that the PCR result is released within a short period of time so that the recipient's treatment is not compromised. It is essential that the result is available before the conditioning regimen begins.

Next, the cost-benefit of such a procedure. Considering the scenario of a viremia rate of 1% in asymptomatic donors, 100 tests would be needed to identify 1 donor with a positive PCR. Donors diagnosed with dengue are deferred from donation and HCT must be postponed.

In view of the above, the Infection Committee of The Brazilian Society for Marrow and Blood Transplantation and Cell therapy (SBTMO) recommends:

1. Guidance for donors and patients who are close to the scheduled date of stem cell (SC) harvesting and preparation for HCT to avoid contact with the vector.

2. Careful investigation of dengue symptoms during pre-transplant assessment. Dengue may initially present as flu-like syndrome.

3. Test all symptomatic donors and recipients, preferably by PCR. Be aware that the sensitivity of NS1

antigen test is lower in first three days of symptoms and in secondary dengue infection[16].

4. PCR is the best test to diagnose dengue in the 1st week of symptoms. In HCT recipients, it is probable that PCR remains positive after the 1st week, due to prolonged viremia observed in this population (13). NS1 is more frequently detected between the 3rd and 5th day of symptoms, and is frequently negative after the 7th day. Serology may be used if PCR or NS1 is not available. IgM generally appears after the 5th day of symptoms[16]. IgG has a limited value in the diagnosis of dengue in endemic countries due to the possibility of previous dengue infection.

5. In the case of a donor with a positive PCR, the period of ineligibility for donation is 30 days for mild cases of dengue, and 180 days if the donor has severe dengue.

6. In the case of a candidate for HCT with a positive PCR, the transplant must be postponed for 30 days after clinical resolution of the disease. Be aware that immunocompromised candidates and HCT recipients may have prolonged viremia[13].

7. Instruct all donors to report fever, malaise, headache or other symptoms that appear in the week following stem cell harvesting. It is important to exclude the possibility that the donor had the SC harvested during the dengue incubation period.

8. During periods of epidemics, it is strongly recommended to include dengue PCR and NS1 test as appropriated, in the investigation of febrile episodes, thrombocytopenia or shock in HCT recipients.

9. The live attenuated dengue vaccine has not been evaluated in immunocompromised patients and is not recommended in HCT recipients. However, close contacts with patients must follow the National Immunization Program (PNI) regarding vaccination against dengue.

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