

**Tisagenlecleucel Infusion in Patients With Relapsed/Refractory ALL and Concurrent
Serious Infection**

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Patient 1

First-line chemotherapy (according to Associazione Italiana Ematologia Oncologia Pediatrica) comprised high-dose cytosine arabinoside (cytarabine [Ara-C]; 6 g twice daily, days 1-4) and mitoxantrone (MTX; 20 mg/day, days 3-5) initiated June 2017. Second rescue therapy with blinatumomab 1 month later elevated the blast count from 3% to 80%. Three rounds of inotuzumab (1.6 mg, 1 mg, 1 mg) were administered. Persistent disease with 95% blast count by flow cytometry was detected. The patient underwent a bone marrow transplant in January 2018. The patient had no sign of graft-versus-host disease but experienced 2 febrile neutropenia episodes, bleeding diatheses, and irregular bowel movements (diarrhea followed by constipation). The patient received Zalmoxis T lymphocytes (TK suicide gene-modified, donor-derived T cells, $1 \times 10^7/\text{kg}$) in February, April, and May 2018 and achieved remission in April and May. Steroids and vincristine (VCR) were initiated 2 months before tisagenlecleucel infusion.

Patient 2

The patient received a standard steroid window of 7 days, resulting in adequate reduction of peripheral blasts. Her induction therapy was 5 doses of VCR, 2 doses of doxorubicin, 8 doses of L-asparaginase, prednisone, and 2 doses of intrathecal triple therapy. The patient achieved minimal residual disease-negative status 12 months before tisagenlecleucel infusion. She continued to receive therapy according to the national Mexican protocol: high-dose MTX, then VAP (Cap-vincristine, doxorubicin, and prednisone) alternating with MTX (2 g/m²/dose). Eight months before tisagenlecleucel infusion, the patient received Ara-C, cyclophosphamide, VCR, and 6-mercaptopurine (6-MP) as her last therapy. A month later, she developed febrile neutropenia and relapsed pre-B-ALL was confirmed. Her bone marrow blast count increased from 40% to 98% in 2 weeks. She received another induction therapy comprising prednisone on days 1-29; VCR on days 1, 7, 15, and 21; L-asparaginase 1000 International Units (IU) on days

2, 9, 16, and 23; doxorubicin 60 mg/m²/dose on day 1; and intrathecal triple therapy on days 1 and 8. Six months before tisagenlecleucel infusion, refractory disease was detected at a blast count of 47%. The patient received blinatumomab for 2 doses. Three months before tisagenlecleucel infusion, 7% blasts were detected. She underwent a third reinduction therapy comprising intrathecal MTX on day 1; dexamethasone 20 mg/m²/day to the end of the month; MTX 10 mg/m²/dose on days 1 and 2; VCR on days 3, 10, 17, and 24; and pegylated *Escherichia coli* (PEG)-asparaginase 1000 IU/m² on days 3 and 15 for 2 months along. The bone marrow aspirate revealed active ALL and the patient was referred for tisagenlecleucel infusion. She received maintenance chemotherapy (6-MP and MTX) along with local radiation (left maxillary sinus) prior to leukapheresis. The patient also had the comorbidity renal Fanconi syndrome before infusion. After infusion, the patient was limited to voriconazole and levofloxacin for antifungal/antimicrobial coverage.