

The Sheba Lung Transplant Program: A Dream Come True

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KEY WORDS: extracorporeal membrane oxygenation (ECMO), lung transplantation, pulmonary fibrosis

IMAJ 2023; 25: 152–153

Twenty years after being closed due to unfavorable results, a new lung transplant program was started at the Sheba Medical Center. The new team included an experienced lung transplant surgeon, an anesthesiologist, an intensive care specialist, and a pulmonologist with extensive experience in the field.

An interdisciplinary team, including nurses, perfusion technicians, nutritionists, psychologist, and physiotherapists received one month of training at one of the biggest lung transplant centers in North America. The first surgery was performed in 2020 and 14 transplants had been conducted by 2021, with no surgical mortality.

Lung transplantation is one of the most complex medical procedures due to the diversity of health professionals involved in the process.

To start a new transplant program in a country that for 20 years had only a single and very active practice, is a very difficult task. Such a project was initiated by the Sheba Medical Center administration in 2019. After recruiting specialists in the field, the infrastructure for the program was built with the help of an interdisciplinary team that included nurses, physiotherapists, nutritionists, psychologists, and perfusion technicians. First, we presented a workshop at Sheba with several exponent surgeons who came from abroad. Next, a group of 16

staff members from Sheba attended an additional one-month training period at one of the most prestigious centers for lung transplantation in North America.

After everything was set, permission from the Ministry of Health was received and the first surgery was conducted in 2020. After the first case, 14 more cases were performed with no 30-day mortality.

PATIENT DESCRIPTION

Our first case was a 14-year-old male who was diagnosed with embryonic carcinoma at another hospital. He received aggressive chemotherapy treatment based on bleomycin and developed pulmonary fibrosis with severe respiratory insufficiency. He developed bilateral pneumothoraces and was attached to mechanical ventilation. On 21 September 2020, he was transferred to the Safra Children's Hospital Intensive Care Unit at the Sheba Medical Center. He was connected to a venovenous (VV) extracorporeal membrane oxygenation (ECMO) [Figure 1A]. During his period at the pediatric intensive care unit, he had several episodes of bilateral pneumothorax with prolonged air leak and very stiff lungs. Transplant was considered the only option for recovery; therefore, he was transferred to the lung transplant team. Although his recent history of malignancy and after consulting other transplant centers, the boy was listed for lung transplantation and kept awake on ECMO while participating in physiotherapy.

Three months after his admission to our medical center, a bilateral lung

transplantation was performed. The procedure was uneventful, and he was weaned from ECMO and mechanical ventilation. Three weeks after surgery, the tracheostomy cannula was removed. Ten months after the surgery, the boy was attending school and no evidence of malignancy was found [Figure 1B].

COMMENT

Lung transplantation in patients with recent malignancy is controversial. The standard of care and guidelines state that no such procedures should be conducted in patients who had been diagnosed with malignancy in the last 5 years. However, several researchers debate these guidelines as lung transplantation may be a viable option in the presence of a recent malignancy [1-3]. The decision to operate on our patient was based on the input given by the oncologists regarding the very low likelihood of recurrence of this specific type of tumor.

Another point of controversy was the long-term ECMO that traditionally, prior to the coronavirus disease 2019 (COVID-19) pandemic, was a contraindication to surgery. The fact that we could keep our patient awake doing physiotherapy helped to maintain his condition as a single organ failure suitable for transplantation [2].

After the initial surgery, we transplanted two post-COVID-19 patients who were connected to ECMO for 3 and 4 months, respectively. Both cases were kept awake on ECMO with no surgical morbidity or mortality.

Figure 1. Chest X-ray

[A] On the day before surgery



[B] Three months after surgery



CONCLUSIONS

The Sheba Lung Transplant Program is now a reality. Since the first case, 10 months after opening the center, 13 cases were performed with no 30-day surgical mortality. We had more than 30 candidates listed for transplantation by 2022, and new technologies have increased the number of transplants and improved the results.

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Music hath charms to soothe a savage breast, to soften rocks, or bend a knotted oak.

William Congreve (1670–1729), English playwright and poet of the Restoration period

Capsule

Multiple pathways for SARS-CoV-2 resistance to nirmatrelvir

Iketani and co-authors examined resistance to nirmatrelvir by in vitro passaging of SARS-CoV-2 in nirmatrelvir using two independent approaches, including one on a large scale. Highly resistant viruses emerged from both, and their sequences showed a multitude of 3CL protease mutations. In the experiment performed with many replicates, 53 independent viral lineages were selected with mutations observed at 23 different residues of the enzyme. Nevertheless, several common mutational pathways to nirmatrelvir resistance were preferred, with a majority of the viruses descending from T21I, P252L, or T304I as precursor mutations. Construction and analysis of 13 recombinant SARS-CoV-2 clones showed that these

mutations mediated only low-level resistance, whereas greater resistance required accumulation of additional mutations. E166V mutation conferred the strongest resistance (around 100-fold), but this mutation resulted in a loss of viral replicative fitness that was restored by compensatory changes such as L50F and T21I. These findings indicate that SARS-CoV-2 resistance to nirmatrelvir arises via multiple pathways in vitro, and the specific mutations observed herein form a strong foundation from which to study the mechanism of resistance in detail and to inform the design of next-generation protease inhibitors.

Nature 2023; 613: 558
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