Imatinib for sclerodermatous graft-versus-host disease in lung transplantation

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INTRODUCTION

Despite medical advances in haematopoietic stem-cell transplantation (HSCT), chronic, progressive and irreversible pulmonary complications after HSCT, such as bronchiolitis obliterans and pulmonary fibrosis, remain the leading causes of death. No effective medical therapy has been established and currently lung transplantation is the only therapeutic option [1]. Sclerodermatous GVHD presents therapeutic challenges, especially for patients with severe skin lesions limiting thoracic movement. Imatinib mesylate, a tyrosine kinase inhibitor, has shown efficacy in the treatment of chronic GVHD, with overall response rates of 50–80% for fibrotic skin symptoms reported in two open-label studies [2]. However, imatinib mesylate theoretically has an adverse effect on wound healing. In lung transplantation, complications related to bronchial anastomoses may be fatal. Herein, we report successful living-donor lobar lung transplantation (LDLLT) in a patient who received treatment with imatinib mesylate for sclerodermatous GVHD in the perioperative period.

CASE REPORT

A 19-year old female patient underwent bone marrow transplantation for the treatment of acute myelogenous leukaemia. Sixteen months later, she developed sclerodermatous chronic GVHD, which was refractory to the usual immunosuppressant therapy. Her movements became severely limited because of the sclerodermatous skin changes, and she was eventually treated with imatinib mesylate 100 mg/day. Subsequently, her skin condition improved; however, she developed pulmonary fibrosis related to her chronic GVHD. Despite treatment with prednisolone and tacrolimus, her pulmonary disease gradually worsened. At the age of 24, a pneumonic process exacerbated her chronic pulmonary GVHD, and she required mechanical ventilation. Her cutaneous disease remained stable when imatinib mesylate was temporarily discontinued during steroid pulse therapy and high-dose prednisone therapy following pulse therapy. Since she was on mechanical ventilation for >3 months without any possibility of weaning from the ventilator, she was referred to our hospital and LDLLT was carried out because of the patient’s extremely poor prognosis. Chest radiography showed severe pulmonary damage due to pulmonary complications after bone marrow transplantation (Fig. 1). Preoperatively, her tidal volume was 2.5 ml/kg, even while being ventilated with bilevel positive airway pressure of 20 and 5 cmH2O, with a respiratory rate of 40 breaths/min. The patient’s father donated a right lower lobe, and her mother donated a left lower lobe. Three weeks before LDLLT, imatinib mesylate was discontinued. LDLLT was successfully carried out with extracorporeal membrane oxygenation. The early postoperative course was uneventful with the exception of an episode of acute rejection on postoperative day 6 requiring treatment with steroid pulse therapy. On postoperative day 7, she complained of a sensation of progressive skin tightness. There were no problems regarding wound healing on the skin and at the bronchial anastomotic sites. Her symptoms were limited to the skin, and we consequently resumed treatment with imatinib mesylate 100 mg/day for an apparent exacerbation of her sclerodermatous GVHD. Within several days of restarting therapy, her cutaneous

Keywords: Lung transplantation • Imatinib • Sclerodermatous graft-versus-host disease

Abstract

Imatinib has been proposed as a treatment for sclerodermatous chronic graft-versus-host disease (GVHD) due to its antifibrotic activity. Because imatinib has a potentially adverse effect on wound healing, the safety of its perioperative use in lung transplantation is unknown. Herein, we present a patient who underwent bilateral living-donor lobar lung transplantation for pulmonary complications after bone marrow transplantation, who had also received treatment with imatinib for sclerodermatous GVHD. Imatinib was discontinued 3 weeks before lung transplantation, but was resumed 1 week postoperatively for an exacerbation of sclerodermatous GVHD. Seven months after the postoperative period the patient continues to do well without complications.
symptoms began to gradually improve. The patient was weaned off
the ventilator 3 weeks after the LDLLT. Postoperative bronchoscopy
showed no complications involving the bronchial anastomoses. She
was discharged home \(\approx 3\) months after the LDLLT. Chest radiog-
raphy showed an excellent lung condition (Fig. 2). Seven months
after the LDLLT, the patient requires no oxygen supplementation,
and her activities of daily living continue to improve.

**DISCUSSION**

With advances in the field of HSCT, the number of patients living
with potentially fatal pulmonary complications after HSCT has also
increased. LDLLT represents an alternative approach to deceased-
donor lung transplantation for such patients in countries where a
severe donor shortage exists, particularly in Japan [1, 3]. In general,
mechanical ventilation is considered as a relative contraindication
for lung transplantation. However, in the current case, the general
condition of the patient gradually recovered because of the
medical treatment during the 3 months when she was on mechani-
cal ventilation. She could even ambulate by herself owing to the
intensive physiotherapy before lung transplantation.

Imatinib mesylate exerts a selective inhibition of the pathways
involved in collagen production in dermal fibroblasts [2]. Imatinib
has recently been proposed as an adjunctive treatment in chronic
GVHD because of its antifibrotic activity [4]. However, because the
antifibrotic effect may adversely affect wound healing, there has
been a concern that it might hinder the healing of bronchial anas-
tomoses in lung transplantation patients. The first study of the
postoperative use of sirolimus, which also has inhibitory effects on
fibroblast proliferation, in lung transplantation reported a high in-
cidence of bronchial anastomotic dehiscence, which in some
cases proved fatal [5]. Experimental studies on everolimus, which
is a derivative of sirolimus, revealed a decrease in traction resist-
ance of bronchial anastomoses that persisted for at least 4 weeks
postoperatively. Although there are no reports on cessation of
imatinib mesylate during the perioperative period, we had

preoperatively planned to resume administration of imatinib
mesylate at least 4 weeks after the LDLLT. Despite the early re-
sumption of therapy, no adverse effect on healing was observed.
Since imatinib mesylate is a promising treatment of scleroderma-
tous chronic GVHD, we will likely encounter more patients being
treated with imatinib mesylate, who are to undergo lung trans-
plantation. Our experience documents the safe and efficacious
use of imatinib mesylate for the treatment of sclerodermatous
GVHD 1 week after lung transplantation. However, the bronchial
anastomosis is carried out at the lobar bronchus of the graft in
LDLLT, leading to a relatively better retrograde blood supply at the
anastomotic site compared with the common brain-dead donor
lung transplantation where the main bronchus is anastomosed.
Therefore, in brain-dead donor lung transplantation, imatinib
mesylate must be used more cautiously because of an inferior
blood supply at the bronchial anastomosis. In this patient, we had
to resume imatinib mesylate earlier than we planned, but we must
be more careful and even aware of the possibility of lethal compli-
cations in resuming imatinib mesylate in patients that have under-
gone brain-dead donor lung transplantation.

**CONCLUSION**

The perioperative administration of imatinib mesylate improved
sclerodermatous chronic GVHD without any apparent deleterious
effect on wound healing, and imatinib mesylate may be used cau-
tiously in patients who have recently undergone LDLLT.

**Conflict of interest:** none declared.

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