Treatment of severe acute lung allograft rejection with OKT3 and temporary extracorporeal membrane oxygenation bridging

Clemens Aigner, Peter Jaksch, Samy Mazhar, Kriztina Czebe, Gabriel Marta, Sharokh Taghavi, Georg Lang, Walter Klepetko*

Department of Cardiothoracic Surgery, University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

Received 16 September 2003; received in revised form 28 October 2003; accepted 10 November 2003

Abstract

Objectives: The use of OKT3 for treatment of advanced high-grade acute rejection episodes eventually can result in cytokine release and consecutive pulmonary edema. Temporary extracorporeal membrane oxygenation (ECMO) bridging can be used to overcome this crucial period before the beneficial effects of OKT3 can be observed. Methods: We summarize our experience with three patients, who underwent lung transplantation and presented with severe acute rejection episodes. OKT3 had to be initiated due to insufficient response to standard rejection therapy with corticosteroids. Upon initiation of OKT3 treatment, a massive life-threatening deterioration of lung function in spite of heavily invasive respirator treatment was seen and temporary ECMO support was imperative to support graft function. Results of this treatment were retrospectively reviewed. Results: In all cases femoro-femoral veno-arterial ECMO was used for support of the impaired graft and after a period of 4–5 days led to a massive improvement of graft function. In the further course two patients could be discharged from hospital and are still alive 30 and 36 months, respectively, after the described incident. One patient died 4 months later due to liver failure. Conclusions: We conclude that the use of ECMO support in patients experiencing significant side effects from OKT3 therapy is a useful and effective therapeutic tool to overcome the initial critical period until the lung has sufficiently recovered.

Keywords: Lung transplantation; Extracorporeal membrane oxygenation; OKT3; Acute rejection; Steroid-resistant rejection

1. Introduction

OKT3 (muromonab-CD3) is a murine monoclonal antibody causing depletion of circulating T lymphocytes by binding CD3-receptor complex located on T cells. It has been used for induction of immunosuppression as well as for treatment of severe acute rejection episodes in all types of solid organ transplants. An especially useful indication was found to be the treatment of severe acute rejection episodes unresponsive to corticosteroids. Yet its application is connected with multiple side effects. Especially when OKT3 is installed in the treatment regimen at a late point in already established severe rejection after lung transplantation, a temporary further deterioration of graft function due to release of cytokines and resulting pulmonary edema has been observed [1]. When this effect is especially pronounced, it can result in a situation where it becomes impossible to maintain adequate oxygenation with conventional ventilation. To overcome the period of time until organ function has recovered, extracorporeal membrane oxygenation (ECMO) bridging can be used as a temporary bridging therapy.

In this report we summarize our experience in three patients, in whom we have treated this pathophysiological constellation with this therapeutic combination.

2. Patients

2.1. Patient 1

A 30-year-old female underwent left single-lung transplantation for idiopathic pulmonary fibrosis. Immunosuppression was initiated by administration of a triple drug therapy consisting of cyclosporin A, mycophenolate mofetil and corticosteroids. Postoperatively the patient...
developed a moderate reperfusion edema, which was managed with a combination of negative fluid balance and increased ventilation pressures and the patient was eventually extubated on the third postoperative day. On the fourth postoperative day, the chest X-ray showed an increased clouding of both lungs, with mainly perihilar infiltrations on the transplanted left side clinically suggestive for an acute rejection episode which was accordingly treated by intravenous application of 1000 mg methylprednisolone for 3 days and concomitant antibiotic prophylaxis. Under this therapeutic regimen a quick improvement of the patients oxygenation together with a normalisation of the X-ray was achieved. However, on the 16th postoperative day new shadowing of the transplanted lung was revealed at X-ray. The patient underwent transbronchial biopsy and rapidly deteriorated thereafter which made re-intubation and aggressive ventilation necessary. Histology proved an acute rejection grade A3, B1 and 500 mg methylprednisolone together with 5 mg OKT3 were administered. Despite negative fluid balance, lung function further deteriorated and 8 h later the transplanted lung became homogenously white on chest X-ray. Under maximal ventilation with FiO₂ 1.0 and high pressures, PaCO₂ rose to 224 mmHg and pO₂ dropped to 60 mmHg. Faced with the impossibility of maintaining an adequate gas exchange by conventional ventilation, femoro-femoral veno-arterial ECMO was initiated.

This resulted in an immediate stabilisation of the hemodynamic situation together with normalisation of oxygenation parameters. Over the following 3 days, with continuation of the daily administration of 5 mg OKT3, a continuous improvement in chest X-ray and oxygenation capacity of the lung was observed. The patient was gradually weaned from ECMO and the device was finally discontinued 4 days after its implantation.

The further course initially was uneventful and the patient was extubated 12 days after re-intubation. Thereafter 30 months, she is still alive in bronchiolitis obliterans syndrome (BOS) stage 0.

2.2. Patient 2

A 48-year-old male received a left single-lung transplantation for idiopathic pulmonary fibrosis. Immunosuppression was initiated by administration of a triple drug therapy consisting of cyclosporine A, mycophenolate mofetil and corticosteroids. He soon developed recurrent episodes of rejection resulting in early onset and rapid progression of obliterative bronchiolitis. All therapeutic efforts like augmentation of immunosuppression and switch from cyclosporin A to tacrolimus were ineffective and 6 months later he underwent single-lung re-transplantation on the left side. Weaning from the respirator was prolonged and the patient was extubated not earlier than the sixth postoperative day. On the eighth postoperative day he presented with temperature up to 39.6 °C and severe tachypnoe. Chest X-ray showed minor shadowing of the lower parts of the left lung. Putrid secretion together with a positive Gram stain found at bronchoscopy was suggestive for a respiratory infection. Antibiotic therapy was expanded to teicoplanin and meropenem and the result of the concomitantly performed transbronchial biopsy had to be awaited. Meanwhile the patient developed massive respiratory and hemodynamic deterioration and chest X-ray showed a homogenously white transplanted lung. Despite maximal ventilation and NO administration it was not possible to maintain sufficient oxygenation, and femoro-femoral veno-arterial veno-arterial ECMO was implanted. When the histological result of the transbronchial biopsy arrived, graft rejection grade A2-A3, B3 was demonstrated. The patient received 1000 mg methylprednisolone together with 5 mg OKT3 intravenously.

Over the next 2 days the patient rapidly stabilised under the maintenance of the OKT3 therapy which was paralleled by a normalisation of the thoracic X-ray (Figs. 1–4). After a total time of 5 days ECMO support, the device was discontinued and the patient thereafter experienced a slow but continuous recovery.

The further course was uneventful and the patient was extubated 8 days after discontinuation of the ECMO and left hospital on the 73rd postoperative day. Thereafter 36 months, he is still alive in BOS stage 0.

2.3. Patient 3

A 32-year-old female underwent bilateral lung transplantation for cystic fibrosis. She experienced primary graft failure and was re-transplanted 1 month later. Immunosuppression consisted of a triple drug therapy including cyclosporine A, mycophenolate mofetil and corticosteroids. The immediate postoperative period was uneventful. From the 10th postoperative day a continuous deterioration of...
the respiratory situation together with the radiological picture was observed. Despite negative histology the clinical situation was strongly suggestive for an acute rejection episode and after exclusion of other potential causes a corticosteroid bolus therapy was administered. This however was followed by further progressive deterioration over the next 2 days. Under the suspicion of corticosteroid refractory rejection OKT3 therapy was initiated. Thereafter a decrease of oxygen saturation down to 80% was observed in spite of maximal invasive ventilation. Hemodynamic instability with hypotensive periods required intravenous catecholamine support and femoro-femoral veno-arterial ECMO was initiated.

Under continuation of the OKT3 therapy and ECMO support an improvement of the respiratory situation and the chest X-ray finding were seen from the first day thereafter. ECMO flow was gradually reduced and the device was explanted after 5 days, at a time when the patient showed a stable respiratory and hemodynamic performance.

The further course of the patient was complicated by prolonged weaning and mobilisation. Recurrent bacterial infection episodes required prolonged antibiotic therapy. In the following 3 months, the patient developed progressive liver failure and despite all therapeutic efforts died due to diffuse haemorrhage.

3. Discussion

Acute rejection episodes are a common complication following lung transplantation. First line standard treatment consists almost uniformly of application of high doses of corticosteroids. For treatment of steroid-resistant rejection episodes monoclonal and polyclonal antibody treatment has successfully been used [2]. OKT3 is the most potent monoclonal antibody which binds CD3-receptor complex on T lymphocytes and depletes circulating T cells within minutes to hours following intravenous administration. Since it leads to complement activation [1] and the release of cytokines IL-1, IL-6 and tumour necrosis factor of T cells and monocytes, its use can be combined with flu-like symptoms including chills, fever, nausea, vomiting, headache, diarrhoea and myalgia. When used for induction therapy it has been reported to be efficient and safe [3]. However, when OKT3 is used in an already established and pronounced acute lung rejection, its immediate effect can cause temporary development of lung oedema and severe hypotension due to the described mechanisms.
This life-threatening situation can occur despite concommitant supportive measures like corticosteroid administration and fluid restriction. Sometimes the effect can be even so severe that maintenance of adequate oxygenation with conventional mechanical ventilation becomes impossible. Temporary femoro-femoral veno-arterial ECMO support remains the only treatment option in this situation until the lung has recovered sufficiently.

In the three patients described no induction therapy had been given and immunosuppression was uniformly initiated with a triple drug combination consisting of cyclosporin A, mycophenolat mofetil and corticosteroids. In one case a switch from cyclosporin A to tacrolimus was performed prior to the described episode due to recurrent acute rejections. In the early postoperative period target trough levels of cyclosporin A were 350–400 ng/ml and of tacrolimus 18–20 ng/ml.

ECMO has been clinically used in pulmonary and cardiopulmonary failure for more than 10 years and is increasingly used in patients after lung transplantation [4,5]. In some centres, ECMO is used intraoperatively instead of cardiopulmonary bypass [6]. Perioperative ECMO support has been described in patients with pulmonary hypertension with the intention to improve initial organ function by controlled reperfusion and less aggressive ventilation [7]. The main indication for ECMO use in the postoperative period however remains acute graft failure [8]. Especially for its use in early graft failure within 24 h after transplantation, impressive results have been reported [9]. However, the use of temporary ECMO bridging for treatment of severe side effects of OKT3 application in advanced lung rejection has not been described in the literature yet.

Without the use of OKT3 all three patients described above would not have survived. Especially during a rapid onset and development of acute rejection, which is typical for situations such as re-transplantation and overcoming of lung reperfusion oedema the application of adequate rejection therapy is sometimes delayed. When therapy is then administered, the potential side effects can be markedly severe. The use of ECMO in this situation not only helps maintain adequate oxygenation and provides hemo-dynamical support but also rather reduces the need for extremely aggressive ventilation and use of high doses of catecholamines. Another important aspect is the continuation of the once-initiated therapy with OKT3 despite the initial clinical deterioration of the patient after its start. Although this temporary critical deterioration of lung oxygenation might raise concerns about the correctness of the diagnosis, it is however an inherent part of the complex situation and treatment. Under continuous ECMO support the recovery of the lung can safely be awaited, however, since blood flow through the lung is mixed with the blood flow from the ECMO device, it is important to ensure adequate brain oxygenation by continuous pulse oxymetry of the right upper limb. The size of the femoral cannulas is usually chosen after exploration of the femoral vessels in order not to compromise the distal femoral artery flow. In case of a small diameter of the vessel and a complete occlusion by the arterial cannula a separate cannulation of the distal limb is performed.

The remarkable improvement in lung oxygenation, paralleled by normalisation of the chest X-ray in all three patients gives evidence of the potential of the lungs to recover from severe immunological damage within a relative short period of time.

We conclude that the use of ECMO support in patients experiencing significant side effects from OKT3 therapy is a useful and effective therapeutic tool to overcome the initial critical period until the lung has sufficiently recovered.

References