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Long term survival after heart transplantation for doxorubicin induced cardiomyopathy

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Abstract

A 10 year old child developed severe cardiomyopathy after combined, multicycle chemotherapy for Ewing's sarcoma and was treated by heart transplantation with good results. Long term azathioprine and cyclosporin caused only mild impairment of immune function and there were no recurrent infections, local recurrences of the tumour, or distant metastases.

Ewing's sarcoma is a malignant, round cell tumour of bone that occurs in later childhood and adolescence, which has a poor prognosis.[1 2] Before the era of combination chemotherapy the five year survival rate was 5 to 10%.[1] Aggressive chemotherapy has resulted in a mean three year disease free survival of almost 60%.[3] This improvement is mainly the result of systemic chemotherapy, with better staging of patients or more efficient radiation regimens playing a small part.

Doxorubicin hydrochloride (Adriamycin) is an essential drug in combined, multicycle chemotherapy,[1 2] although it is known (together with related drugs) to cause a cardiomyopathy that is usually dose dependent.[4]

We describe a child who, having developed a severe cardiomyopathy after combined, multicycle chemotherapy for Ewing's sarcoma, underwent heart transplantation with good results.

Case report

An 8 year old boy with Ewing's sarcoma of the pelvis and proximal femur was treated with a four drug combination of chemotherapy (vincristine, cyclophosphamide, dactinomycin, and doxorubicin hydrochloride), plus local irradiation (protocol POG 8095), and conservative surgery. The total dose of doxorubicin that he received was 480 mg/m^2. Despite regular monitoring of cardiac function by electrocardiography and echocardiograph scanning, severe cardiomyopathy developed 25 months after the diagnosis had been made. Cardiac function rapidly worsened and was soon so impaired that several episodes of congestive failure occurred during the subsequent weeks, leaving the child bedridden.

Twenty nine months after the diagnosis of Ewing's sarcoma and four months after the onset of cardiomyopathy, the child, by then 10 years old and with no evidence of residual tumour, underwent orthotopic transplantation of a heart from an 8 year old child who had been killed in a car accident. The postoperative course was uneventful. Signs of rejection were monitored by serial myocardial biopsies, and prevented by oral immunosuppressive drugs cyclosporin (5 mg/kg/day), methylprednisolone (2 mg/kg/day), and azathioprine (62·5 mg/day). During the next few months the steroids were reduced to 5 mg daily.

More than three years after transplantation the child is doing well: his heart function is normal, he attends school, and he is able to take part in normal physical activities. Repeated checks indicate that there is no local recurrence or distant metastases. His serum immunoglobulin concentrations were: IgG 14·5 g/l, IgA 4·7 g/l, and IgM 1·8 g/l. IgG subclass values were: IgG_1 8·1 g/l, IgG_2 1·8 g/l, IgG_3 1·3 g/l and IgG_4 0·3 g/l. Peripheral blood T lymphocyte subsets were: CD3+ 83%, CD4+ 47%, CD8+ 55%, CD11+ 83%, CD20+ 26%, and CD16+ 6%. Lymphocyte proliferative response to phytohaemagglutinin in vitro was 71·7% of normal controls. Delayed type hypersensitivity skin testing evoked no response to any of the challenged antigens.

Discussion

Ewing's sarcoma is a malignant bone tumour that had a poor prognosis until combined chemotherapy including anthracyclines was introduced. The current five year disease free survival rate is about 60%. Bacci *et al* recently reported a 7% risk of late relapse after that time, confirming other reports.[3]

We have reported a child who, 25 months after the diagnosis of Ewing's sarcoma, had achieved persistent local and systemic control but suffered from life threatening cardiomyopathy. The decision to attempt heart transplantation was difficult to take. On the one hand it was indicated because of the poor

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quality of the child's life and the lack of any other possible cure for his severe cardiomyopathy; on the other hand his underlying malignant disease was a major obstacle. Now, more than three years later, that choice seems to have been correct. The child has regained a completely normal life: he attends school, has normal heart function, and is able to take part in normal physical activities.

Because of the improvement in cure rate provided by combined treatment of some childhood cancers, the limits for indication of organ transplantation may well be revised. We are aware that a few children with cancer have recently undergone heart transplantation (J Le Bidois, Paris, personal communication[4]), and this treatment is also being given for some non-malignant chronic diseases of children.[5]

The mechanisms of development of distant tumour metastases are not yet completely clarified. A possible role for immune surveillance has been postulated but is still under investigation. In the present case long term immunosuppressive drugs, given to prevent graft rejection, could cause some depression of the immune system, and possibly enhance the risk of tumour recurrence. To assess the real degree of immune depression we had induced in this patient, we tested his immune function. Humoral immunity, assessed by serum immunoglobulin concentrations, was normal. Cellular immunity was also substantially normal. Only the delayed type hypersensitivity skin test reactions, reliable markers of overall immune function, were persistently depressed, as is also seen in children undergoing chemotherapy for leukaemia.

To conclude, heart transplantation succesfully cured doxorubicin induced cardiomyopathy despite the underlying tumour. Long term administration of steroids, azathioprine, and cyclosporin caused only mild impairment of immune function; he had no recurrent infection, local recurrence of tumour, or distant metastases.

With continuing advances in our understanding of tumour biology and the techniques of organ transplantation, eligibility criteria for transplantation should continually be re-evaluated. Nevertheless further experience is necessary before this becomes the accepted treatment.

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Life threatening 'epilepsy'

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Abstract

A 5 year old girl presenting with episodes of sudden loss of consciousness was found to have intermittent ventricular tachycardia and, on one occasion, self limiting fibrillation. Corrected QT interval was normal. After several therapeutic measures clinical and electrocardiographic improvement was achieved by administration of sotalol.

We present the case of a girl with a sudden loss of consciousness that was thought to be caused by epilepsy.

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Case history

The patient, a 5 year old girl, was admitted to hospital having collapsed at home. She was found by her mother unconscious, limp, and cyanosed. She had been incontinent of urine and faeces. She recovered after four minutes and appeared confused. She had been born after 42 weeks' gestation by caesarean section for fetal distress evidenced by meconium staining. She had been referred to a paediatric neurologist at 3 years of age with a history of never running. The only abnormalities at that time were mild generalised hypotonia and a slightly broad based gait suggestive of a mild degree of ataxia. Her physical state was thought to be in keeping with a benign congenital hypotonia. At nursery she was noted to have poor fine hand movements and was referred for occupational therapy. Fifteen days before this admission she had tripped and banged her head on the floor. She was then unconscious for four minutes. Skull radiography had shown no fracture and observations overnight in hospital had been normal. A cousin had been investigated for recurrent hypoglycaemia when aged 2 years and ketotic hypoglycaemia diagnosed.

On admission she was fully conscious and alert. Her height was on the 97th centile and weight on the 75th. Cardiovascular, respiratory, and abdominal examinations were normal. She