Successful induction and consolidation therapy of acute myeloid leukaemia in a renal allograft recipient

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Abstract

Immunosuppressed organ transplant recipients have a markedly increased risk of neoplasia. Among these malignancies acute myeloid leukaemia (AML) is rare. However, until now no case of successful chemotherapy has been reported. We present a 39-year-old male patient who developed AML (FAB M4 Eo) 4 years after renal transplantation and achieved a stable complete remission after induction therapy with standard dose cytarabine and daunorubicin. Remission duration is now 11 months. At present the transplant is functioning well after two additional courses of consolidation chemotherapy with high-dose cytarabine combined with mitoxantrone and idarubicine respectively. Cyclosporin A was given during all cycles of chemotherapy. We conclude that intensive chemotherapy in patients with AML following renal transplantation in good performance status is feasible.

Key words: acute myeloid leukaemia; chemotherapy; immunosuppression; infections; renal transplantation

Introduction

The increased incidence of malignancy in immunosuppressed organ transplant recipients (mostly renal transplantations) has been documented in numerous studies. The most frequent tumours are carcinomas of the skin and the urogenital tract and malignant lymphomas. It is not clear whether the incidence of acute leukaemia is also increased in comparison to the normal population. Penn [1] observed a frequency of 2.3% of all types of leukaemia among all malignancies reported to the Cincinnati Transplant Tumor Registry. However, these cases were not specified with regard to acute or chronic leukaemia and myeloid or lymphatic origin. To our knowledge only eight case reports on AML following renal transplantation have been published until now [2–9] (Table 1). All patients died during induction or early consolidation therapy of refractory leukaemia, or from infectious complications. We report on a patient who developed AML 4 years after renal transplantation and achieved a complete response to chemotherapy.

Case report

Our 39-year-old male patient suffered from chronic renal failure secondary to end-stage polycystic kidney disease. He was first haemodialysed in May 1983. In August 1991 he received a cadaveric kidney transplant. The donor was not HLA compatible. Immunosuppression consisted of cyclosporin A 300 mg/day, azathioprine (starting with 100 mg/day, tapering to 25 mg/day), and prednisone (finally 7.5 mg/day). There was no episode of rejection, and the patient did well until October 1995, when he developed fever and malaise. The white blood cell count (WBC) was 10.9 g/l and the peripheral blood smear showed 13% blasts and 65% monocytes. The haemoglobin was 10.6 g/dl and the platelet count was 59 g/l. Bone marrow biopsy showed 70% blasts and an increase in eosinophils. The diagnosis was acute myelomonocytic leukaemia FAB M4 Eo (subtype according French–American–British criteria: acute myelomonocytic leukaemia with an increase of eosinophils). Cytogenetic analysis revealed an inversion of the chromosome 16 (inv (16)). The renal transplant was functioning well. Creatinine was 1.3 mg/dl, blood urea nitrogen (BUN) 50 mg/dl, and the creatinine clearance 70 ml/min.

The patient received induction chemotherapy (cytarabine (100 mg/m² on days 1+2 as continuous infusion + 100 mg/m² b.i.d. i.v. on days 3–8) and daunorubicin (60 mg/m² i.v. on days 3–5)), and complete remission was documented on day 24 by bone marrow aspiration. Seven days after the end of the neutropenic phase the first consolidation chemotherapy consisting of high-dose cytarabine (3000 mg/m² b.i.d. i.v. on days 1–3) and mitoxantrone (10 mg/m² i.v. on days 3–5) was administered. Three weeks after bone marrow recovery from this course a second consolidation therapy with the same cytarabine dosage but idarubicin (12 mg/m² i.v. on days 3–5) instead of mitoxantrone...
Table 1. AML in renal transplant patients (case reports)

<table>
<thead>
<tr>
<th>Author</th>
<th>FAB</th>
<th>Latency after Tx (years)</th>
<th>Chemotherapy</th>
<th>Survival after start of chemotherapy</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pickler et al. [2]</td>
<td>M5</td>
<td>4</td>
<td>HU ADR 45 mg/m² d 1–3+, AraC 100 mg/m² d 1–7</td>
<td>16 days</td>
<td>Refractory</td>
</tr>
<tr>
<td>Butler et al. [3]</td>
<td>M7</td>
<td>5</td>
<td>ADR + 6-TG</td>
<td>22 days</td>
<td>Refractory</td>
</tr>
<tr>
<td>Cuthbert et al. [4]</td>
<td>M4</td>
<td>1</td>
<td>DNR AraC 6-TG (3 +10) DNR AraC 6-TG (2 +7) mid-dose AraC d 1–3/ Mit d 1–5</td>
<td>10 weeks</td>
<td>Sepsis (pseudomonas)</td>
</tr>
<tr>
<td>Hoy et al. [5]</td>
<td>M6</td>
<td>7</td>
<td>4 courses (not specified)</td>
<td>7 months</td>
<td>Refractory (CNS)</td>
</tr>
<tr>
<td>Ellerton et al. [6]</td>
<td>M6</td>
<td>3</td>
<td>DNR AraC 100 mg/m² d 1–7</td>
<td>6 days</td>
<td>Septic shockenterococcolis</td>
</tr>
<tr>
<td>Sweeney et al. [7]</td>
<td>M6</td>
<td>8</td>
<td>HU DNR (one course)</td>
<td>11 weeks</td>
<td>Intracerebral haemorrhage</td>
</tr>
<tr>
<td>Hand et al. [8]</td>
<td>M4</td>
<td>6</td>
<td>None CYC/VCR/AraC/PRD 3 courses</td>
<td>2 weeks</td>
<td>Progression</td>
</tr>
<tr>
<td>Leithner et al. [9]</td>
<td>M0–2?</td>
<td>8</td>
<td>CYC/VCR/AraC/PRD 3 courses</td>
<td>8 weeks</td>
<td>Sepsis (streptococcus)</td>
</tr>
</tbody>
</table>

Tx, transplantation; ADR, doxorubicin; DNR, daunorubicin; AraC, cytarabine; HU, hydroxyurea; 6-TG, 6-thioguanine; Mit, mitoxantrone; PRD, prednisone; CYC, cyclophosphamide; VCR, vincristine; refractory, leukaemia refractory to chemotherapy.

was given. Filgrastim (recombinant human granulocyte colony-stimulating factor) (480 mg/day) was administered after every cycle. The duration of the neutropenic phases (WBC < 1 g/l) was short after induction therapy (15 days) and first consolidation therapy (16 days), but prolonged following the second consolidation therapy (31 days).

Immunosuppression was reduced before the start of chemotherapy. Azathioprine was discontinued. Prednisolone was temporarily discontinued, but reinstated with 5 mg/day after the end of the neutropenic phases. Cyclosporin A was reduced to 50–75 mg/day to avoid accumulation due to interaction with itraconazole and to maintain a serum level of approximately 80 ng/ml (lower limit of the therapeutic range in our monoclonal assay). Antimicrobial prophylaxis and selective gut decontamination was performed with co-trimoxazole (960 mg b.i.d.), colistin (200 mg t.i.d.), and itraconazole (200 mg t.i.d.). Fever of unknown origin (> 38 °C) occurred after induction and after the first consolidation therapy. It resolved in both cases under antibiotic therapy with piperacillin and tazobactam (4.5 g t.i.d.) within 5 and 3 days respectively. The most serious infectious complication was pneumonia with 10 days of fever due to an unknown causative agent after the second consolidation therapy. Piperacillin/tazobactam (4.5 g t.i.d.) alone and in combination with gentamicin (5 mg/kg/day) was not effective. A combination of teicoplanin (400 mg/day), erythromycin (4* 1 g/day) and imipenem/cilastin (1 g t.i.d.) led to complete regression of pneumonia.

In the first week after admission the patient developed a moderate impairment of renal function (increase in creatinine up to 2.4 mg/dl). Renal function normalized following intensification of intravenous fluid load, alkalization of urine, administration of allopurinol, and elimination of leukaemic blasts from circulation.

Now, 11 month after diagnosis of AML, the patient is in good health and continuing in complete remission. Renal function improved compared to status before chemotherapy (recent creatinine clearance 106 ml/min, creatinine (serum) 0.9 mg/dl). At present no further chemotherapy is planned.

Discussion

Acute myeloid leukaemia in patients following renal transplantation leads to a difficult situation. Intensive cytostatic treatment is needed to reduce the leukaemia load as much as possible and to give the organism a chance to control the leukaemic clone. Compared to other patients transplant recipients may be less capable to achieve this. However, these patients tolerate intensive treatment poorly due to fragile kidney function and an increased risk of infections, including Pneumocystis carinii and invasive fungal infections. To our knowledge no case of successful therapy has been reported [2–9] (Table 1). These discouraging results may suggest guarding against chemotherapy with a curative intent. However, our case shows that renal transplant patients may tolerate even a high-dose cytarabine therapy and a neutropenic phase of several weeks. The patient should be in a good performance status. Effective antibiotic and antymyotic prophylaxis and consistent therapy of infections are essential.

Our patient showed an impairment of renal function tightly correlated to rising WBC count before the start of chemotherapy. Major nephrotoxic side-effects by high-dose cytarabine, daunorubicin, idarubicin, and mitoxantrone have not been reported, and were not
observed in our patient. Therefore cytostatic therapy should not be delayed when diagnosis is confirmed and appropriate hydration and alkalinization of urine are provided.

Continuation of immunosuppression is necessary as T-cell function may not be completely suppressed by cytostatic therapy. We monitored CsA serum levels daily (monoclonal assay), since chemotherapy-associated mucositis may cause impairment of drug-resorption, and itraconazole was used for antifungal prophylaxis. The latter drug has been shown to reduce metabolism of CsA by inhibition of microsomal liver enzymes, especially cytochrome P450 3A4.

It has been shown that CsA inhibits cellular efflux of anthracyclines by inhibition of p-glycoprotein 170 and thus increases the intracellular concentrations of these cytotoxic drugs in leukaemic cells. However, controlled clinical trials in AML patients are not yet available. It is not clear to what extent administration of cyclosporin A during chemotherapy may have contributed to the response in our patient.

The subtype FAB M4 Eo of our patient is invariably associated with abnormalities of the chromosome 16. These patients have a better prognosis than those with normal karyotype or most other cytogenetic abnormalities, especially when consolidated with high-dose cytarabine. Therefore risk-adapted treatment based upon cytogenetic analysis has been proposed [10].

Our patient developed AML 4 years after renal transplantation. This approximates the mean latency period of the reported cases (Table 1). An elevated incidence of AML has not clearly been shown in renal transplant patients. However, a causal role of immunosuppression in leukaemogenesis has to be taken into consideration, since several malignant tumours are more frequent after transplantation. Several hypotheses have been provided for explanation. Probably the most important factor is suppression of immune surveillance of tumour cells (and oncogenic viruses) by drugs such as CsA and azathioprine. They act predominantly on T-helper and cytotoxic T cells. Moreover, azathioprine as an antimetabolite may have mutagenic properties. Theories that immunosuppression caused by pre-existing uraemia or chronic antigen stimulation by the transplant are involved in the development of malignant tumours are more speculative.

We conclude that despite the increased risk of infection, intensive chemotherapy in patients with AML following renal transplantation in good performance status is feasible. Although this may pose a threat to the renal graft, our experience is that intensive chemotherapy and maintenance of transplant function is not a contradiction.

Acknowledgements. M. Gorschützer was recipient of a grant from the Leukämie-Initiative Bonn e.V.

Note added in proof

October 1996, 12 months after primary diagnosis a relapse of acute myeloid leukaemia occurred. The patient was treated with high-dose cytarabine (1000 mg/m² i.v. b.i.d., d 1–3) and idarubicin (12 mg/m² i.v. d 3–5). Neutropenia was complicated by septic shock but complete remission could be achieved and the patient is still alive. After bone marrow recovery autologous peripheral blood stem cells were harvested. A stem cell supported consolidation chemotherapy is planned.

References


Received for publication: 4.9.96
Accepted in revised form: 30.10.96