


CASE REPORT

Successful kidney transplantation in a patient with pre-existing chronic myeloid leukemia treated with imatinib

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Active malignancy is an absolute contraindication to kidney transplantation. As for chronic myeloid leukemia (CML), a Philadelphia chromosome-positive myeloproliferative neoplasm, the introduction of tyrosine kinase inhibitors has transformed CML from a lethal into a manageable chronic disease with a close-to-normal life expectancy. To date it is unknown whether kidney transplantation can be safely performed in patients with pre-existing CML. We describe the clinical course of a 57-year-old male patient with chronic kidney disease caused by reflux nephropathy. This patient had undergone first kidney transplantation 20 years earlier and had again been on chronic hemodialysis for 6 years when CML was diagnosed. First-line therapy with 400 mg imatinib daily was well tolerated and induced an optimal cytogenetic and molecular response 3 months after initiation. One and a half years after CML diagnosis, a second kidney transplantation from a deceased donor was performed. Immunosuppression included basiliximab, tacrolimus, mycophenolate mofetil, and corticosteroids. Currently, 2 years posttransplant, renal allograft function is stable (serum creatinine 1.09 mg/dL, estimated glomerular filtration rate 75 mL/min per 1.73 m²), and CML remains in deep molecular remission with imatinib. Imatinib-treated CML in deep molecular remission could be regarded as inactive malignancy and may therefore not be viewed as an absolute contraindication to kidney transplantation.

KEYWORDS

cancer/malignancy/neoplasia: hematogenous/leukemia/lymphoma, clinical decision-making, clinical research/practice, hematology/oncology, kidney disease, kidney transplantation/nephrology, retransplantation

1 | INTRODUCTION

Active malignancy is an absolute contraindication to organ transplantation. For solid tumors, different guidelines on the evaluation

of transplant candidates suggest waiting periods of 2-5 years between successful cancer therapy and organ transplantation depending on the type, staging, and grade of cancer, and its potential for posttransplant recurrence.^{1,2} However, it is less well defined how to

Abbreviations: BCR-ABL, breakpoint cluster region-abelson; CML, chronic myeloid leukemia.

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TABLE 1 Hematological and chemical laboratory data after initiation of imatinib and second kidney transplantation

Months after starting imatinib	0	3	6	9	12	15	18	21	24	27	30	33	36	42	
Months after transplantation		0.5	3	6	9	12	15	18	24	30	36	42	48	54	
Hematologic response															
White blood cell count (4.0-9.0 g/L)	19.3	12.3	11.3	9.4	10.3	11.6	19.0	9.4	12.4	11.0	14.2	10.8	10.5	12.8	
Neutrophils (50%-70%)	78.9	79.0	71.4	73.4	75.0	74.4	85.1	74.0	81.6	77.0	84.0	77.6	79.2	82.9	
Hemoglobin (13.5-17.5 g/dL)	9.3	12.7	14.7	12.1	13.8	9.6	9.2	11.2	12.3	12.9	13.9	13.1	13.7	13.6	
Platelets (130-400 g/L)	699	540	411	384	312	430	461	388	366	310	357	364	331	334	
Cytogenetic response															
No. of Ph+ metaphases in bone marrow	8/20	0/20													
Molecular response			MR ³	MR ⁴	MR ⁴	MR ⁴	MR ⁴	MR ⁵	MR ⁴	MR ⁴	MR ^{4.5}	MR ^{4.5}	MR ^{4.5}	MR ^{4.5}	
BCR-ABL IS (%) in peripheral blood	25	0.4	0.02	0.01	0.0066	0.0049	0.0056	0.00089	0.0061	0.0064	0.003	0.003	0.003	0.003	
Renal allograft function															
Serum creatinine (mg/dL)							1.87	1.40	1.26	1.30	1.22	1.23	1.04	1.09	
eGFR (mL/min per 1.73 m ²)							40	56	63	61	66	65	79	75	
Immunosuppression															
Tacrolimus trough level (ng/mL)							12.8	10.0	5.9	6.2	7.5	5.6	4.1	4.6	
Tacrolimus dose (mg/d)							6	1.5	1	1	1	2	1	1	
Mycophenolate mofetil (mg/d)							2000	2000	2000	2000	2000	1000	1000	1000	
Prednisolone (mg/d)							20	5	2.5	2.5	5	5	5	5	

Treatment monitoring in patients with chronic myeloid leukemia includes assessment of (1) hematologic, (2) cytogenetic, and (3) molecular response. (1) Complete hematologic response as indicated by improved complete blood cell and differential cell counts occurred 3 mo after treatment start. (2) By cytogenetic testing the number of bone marrow cells in metaphase carrying the Philadelphia chromosome (Ph+) is assessed. The absence of the Philadelphia chromosome after 3 mo indicates complete cytogenetic response. (3) The most sensitive method of monitoring residual disease is measuring the level of breakpoint cluster region-abelson (BCR-ABL) transcript in peripheral blood by quantitative reverse-transcriptase polymerase chain reaction as an indicator of the number of circulating leukemic cells. Molecular response is assessed according to the International Scale (IS) as the ratio of BCR-ABL transcripts to the control gene ABL expressed as BCR-ABL IS % on a log-scale. A BCR-ABL transcript level $\leq 0.1\%$ reflects a ≥ 3 log-reduction of BCR-ABL mRNA transcripts and corresponds to a molecular response MR³ (also referred to as major molecular response). Accordingly, a BCR-ABL transcript level $\leq 0.01\%$, $\leq 0.0032\%$, and $\leq 0.001\%$ corresponds to a MR⁴, MR^{4.5}, and MR⁵, respectively (also referred to as deep molecular response). Reference ranges are indicated in parentheses. eGFR denotes estimated glomerular filtration rate calculated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

manage transplant candidates with hematological malignancies such as chronic leukemia because of the rare nature of and consequently limited experience with these diseases in the transplant setting.

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by reciprocal translocation between chromosomes 9 and 22, the so-called Philadelphia chromosome, leading to the formation of the breakpoint cluster region-abelson (BCR-ABL) fusion oncogene. BCR-ABL encodes a persistently activated tyrosine kinase causing enhanced proliferation, differentiation arrest, and resistance to cell death of leukemia cells.³ Without treatment, CML slowly progresses from a chronic to a more aggressive accelerated phase and finally to blast crisis, which, like acute leukemia, is associated with a poor prognosis and without therapy is inevitably fatal.³ With the introduction of a selective inhibitor of the BCR-ABL tyrosine kinase, imatinib mesylate, a targeted therapy has become available,⁴ which has transformed CML from a fatal disease into one that, if treated effectively, is associated with a close-to-normal life expectancy.⁵

Among transplant patients, the incidence of CML is higher compared with the general population.^{6,7} So far, a limited number of cases of solid organ transplant recipients who were diagnosed with CML posttransplant and successfully treated with imatinib has been published.⁸ Herein, we report the first case of a patient with pre-existing CML who underwent successful second kidney transplantation under ongoing imatinib therapy, and discuss potential risks and benefits of transplantation in the context of a myeloproliferative malignancy.

2 | CASE REPORT

In December 1996, a 34-year-old man developed end-stage renal disease caused by reflux nephropathy after he had had several surgical procedures to correct ureteral abnormalities in early childhood and eventually had undergone bilateral nephroureterectomy in a 2-stage procedure. He was treated with hemodialysis from December 1996 until October 1999, when he received his first kidney transplant from a 56-year-old deceased donor who died of a cerebrovascular accident (serum creatinine 1 mg/dL, HLA-A, -B, -DR-mismatch: 2-2-0, cold ischemic time: 13.5 hours). Immunosuppression included basiliximab, cyclosporine A, mycophenolate mofetil, and corticosteroids. One year posttransplant, cyclosporine A was switched to tacrolimus because of gingival hyperplasia. In October 2010, he reentered the chronic hemodialysis program because of histologically proven chronic cell-mediated rejection and allograft failure. At that time, immunosuppressive therapy was gradually reduced and finally discontinued in 2015.

In 2015, a mild but persistent left-shifted leukocytosis occurred with a white blood cell count between 10 and 20 g/L, with 75%-85% of neutrophils, 5%-15% of lymphocytes, 5%-10% of myelocytes, and 1%-3% of metamyelocytes, and further hematological work-up was initiated. Bone marrow examination revealed hypercellular bone marrow with a slightly increased ratio of myeloid/erythroid precursors but no elevation of blasts, consistent with a myeloproliferative disease. Fluorescence in situ hybridization analyses of bone marrow

revealed a novel variant translocation involving chromosome 11 in addition to chromosome 9 and 22 (46, XY, t(9;22;11)(q34;q11;q23)) with the presence of the Philadelphia chromosome in 8 of 20 metaphases. Reverse transcription polymerase chain reaction confirmed the presence of the classical BCR-ABL transcript; thus, diagnosis of CML in chronic phase was established. No hepatosplenomegaly was present, allocating the patient to the low-risk category according to the Sokal Score (including age, spleen size, peripheral platelet and blast count), the European Treatment and Outcome Study (EUTOS) score (including spleen size and peripheral basophil count), and the EUTOS Long-Term Survival score (including age, spleen size, peripheral blast, and platelet count). In April 2016, treatment with the tyrosine kinase inhibitor imatinib at 400 mg/d was initiated. Three months after treatment initiation, the patient achieved a complete hematological response (evaluated by complete blood cell and differential cell counts, and spleen size) associated with a reduction of the BCR-ABL transcripts by 2-log units and a complete cytogenetic remission as confirmed by the absence of the Philadelphia chromosome in bone marrow metaphases. After 6 months of therapy, a major molecular remission (ie, a 3-log reduction of BCR-ABL transcripts in peripheral blood), and another 3 months later a deep molecular remission (ie, an at least 4-log reduction of BCR-ABL transcripts in peripheral blood) were obtained and have been maintained since then (Table 1).

Given the optimal response to imatinib treatment with a stable course of disease and the patient's good general state of health despite significant comorbidities such as arterial hypertension, insulin-dependent diabetes mellitus, coronary artery disease, asymptomatic peripheral arterial disease, and cerebrovascular disease with a history of stroke, the patient was considered eligible for retransplantation. In October 2017 (ie, 1.5 years after initiation of imatinib therapy), he received a second kidney transplant from a 52-year-old deceased donor who died of a traumatic brain injury (serum creatinine 0.62 mg/dL, HLA-A, -B, -DR-mismatch: 2-1-0, cold ischemic time: 23 hours). Immunosuppression included basiliximab, tacrolimus, mycophenolate mofetil, and corticosteroids. Tacrolimus target trough levels were adjusted to 10-12 ng/mL during the first 3 months, to 8-10 ng/mL after the third month until the end of the first year, and to 6-8 ng/mL thereafter.

Currently, the follow-up period after the second kidney transplantation is 24 months. The most recent BCR-ABL monitoring revealed a persistent deep molecular response under ongoing treatment with 400 mg/d of imatinib. The posttransplant course was uneventful, with no delayed graft function, acute rejection episode, or surgical or infectious complications having occurred. Renal allograft function is excellent (serum creatinine 1.09 mg/dL, estimated glomerular filtration rate 75 mL/min per 1.73 m² as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation). Tacrolimus trough levels approximated the target range throughout the follow-up period. The most common side effects of imatinib are cytopenia, fluid retention, gastrointestinal symptoms, muscle cramps, skin rash, and fatigue, none of which occurred in our patient. Furthermore, we had no difficulties in dosing of immunosuppressants (Table 1).

3 | DISCUSSION

To our knowledge, this is the first report of a patient with pre-existing CML who underwent successful kidney transplantation as early as 9 months after he had achieved deep molecular remission under imatinib therapy.

For transplant candidates with leukemia, the American and Canadian Societies of Transplantation in their guidelines propose a waiting time of at least 2 years from successful treatment to transplantation.^{1,2} These guidelines were published 15 or even more years ago, when experience with tyrosine kinase inhibitors was limited. Today, almost 20 years after the approval of imatinib, it is safe to say that tyrosine kinase inhibitors have revolutionized treatment of CML and have markedly improved the prognosis for these patients. For patients with CML under long-term treatment with imatinib, estimated progression-free and overall survival rates at 10 years were reported to be >80%,⁹ and even close to 100% in patients who had a major molecular remission at 12 months and those with a low-risk Sokal Score.¹⁰ Survival among patients with CML is currently considered to be driven by comorbidities rather than CML itself,¹¹ with a 10-year probability of death due to CML of 6% vs 12% for death unrelated to CML.¹² Therefore, in the case of CML, the suggested waiting time of 2 years between treatment and transplantation should certainly be considered a subject of debate. The 2018 Kidney Disease Improving Global Outcomes clinical practice guideline on the evaluation and management of candidates for kidney transplantation is currently updated and will likely propose recommendations regarding transplant eligibility of patients with prior cancers, including hematological malignancies.

Another aspect that we considered of particular relevance when evaluating our patient for transplant eligibility was the role of the immune system in the natural course and therapeutic success of CML, a subject that is currently not well understood. Epidemiological studies suggest an increased risk for CML after solid organ transplantation compared with the general population with standardized incidence ratios between 2.3 and 3.5.^{6,7} In the largest study published to date, Gale and Opelz found 25 excess cases of CML among >440 000 kidney, liver, and heart transplant patients with >2 000 000 patient years at-risk compared with the general population (corresponding to an absolute number of 56 vs 31 CML cases).¹³ CML incidence among transplant patients, however, might be overestimated because of a diagnostic access bias resulting from frequent clinical and blood examinations that are routinely performed among transplant patients but not the general population. Interestingly, even though leukemia occurred more frequently among patients with end-stage renal disease compared with the general population, incidence rates did not differ between kidney function intervals (ie, time with a transplant) and nonfunction intervals (ie, waitlist or time after transplant failure),¹⁴ suggesting that pharmacological immunosuppression probably may not be as important for this type of cancer and that immunosurveillance may only marginally contribute to the natural course of CML. Which other factors may contribute to the increased risk of CML and other hematologic cancers among patients with

end-stage renal disease is not well understood.¹⁵ Basically, hematologic malignancies can be transferred by solid organ transplantation as has recently been reported for donor-derived B cell acute lymphoblastic leukemia¹⁶ or donor-derived multiple myeloma¹⁷ after kidney transplantation. However, the possibility of a donor-derived origin of CML in our patient could be ruled out by DNA typing using a 16-loci short tandem repeat multiplex system (PowerPlex® 16 HS System, Promega, Madison, Wisconsin), which revealed an unmixed microsatellite profile with complete match between bone marrow taken at initial diagnosis of CML and different other tissues (colon, prostate) of the same patient.

Imatinib was designed to specifically target the BCR-ABL tyrosine kinase. However, by also affecting other off-target kinases, imatinib was shown to modulate immune responses and inhibit fibrogenesis in different experimental models of immune-mediated kidney injury. As such it may beneficially affect the progression of certain types of kidney diseases including diabetic nephropathy, nephroangiosclerosis, lupus nephritis, and chronic allograft nephropathy.¹⁸ Whether imatinib has contributed to the excellent renal allograft function in our patient is hypothetical. Regarding safety aspects, long-term studies of imatinib for CML have not revealed any concerns about cumulative or late toxic effects.¹⁰ Currently, safety data for second- and third-generation tyrosine kinase inhibitors in patients with advanced stages of chronic kidney disease and under renal replacement therapy are lacking. In our patient, imatinib was well tolerated, both while on dialysis and after transplantation, and we did not have any difficulties in achieving tacrolimus target levels. Notably, the dose of tacrolimus required to achieve target trough levels was lower after the second kidney transplantation compared with the first one, which might be indicative of an interaction between tacrolimus and imatinib because both of them are metabolized by the hepatic cytochrome P450 enzymatic system.¹⁹

In the presented case, we concluded that the projected benefit (in terms of survival and quality of life) of undergoing a second kidney transplantation would outweigh the potential risk of accelerated progression of CML posttransplant. The fact that the patient was classified as low risk and showed an optimal treatment response with sustained deep molecular remission suggests a favorable clinical course and long-term prognosis. As such, when remaining on lifelong dialysis, survival of this patient eventually is determined by end-stage renal disease and its concomitant diseases. According to the US Renal Data System Report, the expected remaining lifetime of a male diabetic chronic hemodialysis patient of similar age is estimated to be 6.7 years, and is expected to increase by 9.8 years when undergoing kidney transplantation.²⁰ As CML most frequently occurs in the middle-aged population between 50 and 60 years, corresponding to the median age of the transplant population, we will certainly have to face similar decisions with increasing frequency in the future. It ultimately remains an interdisciplinary and patient-centered assessment on a case-by-case basis with thorough balancing between the accelerated mortality when remaining on lifelong dialysis treatment, the expected benefits of kidney transplantation, and the projected risk of cancer recurrence or acceleration.

In conclusion, CML in sustained deep molecular remission under imatinib treatment could be regarded as inactive malignancy and may therefore not be viewed as an absolute contraindication to kidney transplantation.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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