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Case Report

Is Kidney Transplantation a Relative Indication for Patients with Chronic Myeloid Leukemia (CML) in Sustained Remission with Imatinib?

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ABSTRACT

Currently, kidney transplantation is absolutely contraindicated for patients with Chronic Renal Failure (CRF) with active malignancy. However, there is controversy as to whether kidney transplantation can be safely performed in patients with a history of Chronic Myeloid Leukemia (CML) in remission. In this report, a 64-year-old male patient was diagnosed with CML approximately 17 years ago, achieved cytogenetic and molecular remission promptly after starting Imatinib, and remained in remission for more than 15 years with Imatinib therapy. However, Chronic Kidney Disease (CKD) due to DMN gradually worsened, and the patient underwent preemptive living donor kidney transplantation in July 2020. Imatinib for CML was discontinued because the patient maintained Deep Molecular Remission (DMR) of Major Molecular Response (MMR) for more than 15 years prior to kidney transplantation. After the kidney transplantation, the transplanted kidney function remained good at around serum Creatinine (s-Cr) 1.1 mg/dL without histopathological rejection, and the 3 monthly BCR-ABL1 measurement results were negative and are in progress. Thus, he continues to maintain Treatment-Free Remission (TFR) status without imatinib for 35 months after kidney transplantation. In conclusion, this result suggests that CML with long-lasting DMR on imatinib therapy can be considered an inactive malignancy and therefore a relative indication for kidney transplantation.

Keywords: Living donor kidney transplantation; Chronic Myeloid Leukemia (CML); BCR-ABL1; Deep Molecular Remission (DMR); Major Molecular Response (MMR); Treatment Free Remission (TFR)

INTRODUCTION

Kidney transplantation is a medical procedure that offers a life-saving solution for individuals with end-stage renal disease. However, the question of whether kidney transplantation is a relative indication for patients with Chronic Myeloid Leukemia (CML) in sustained remission with Imatinib, a targeted therapy for CML, warrants careful consideration. This complex issue involves balancing the potential benefits of renal transplantation against the risks associated with CML recurrence or complications due to immunosuppressive regimens. This study includes the need for a comprehensive evaluation of patient-specific factors, including the stability of CML remission, overall health status, and potential interactions between immunosuppressive drugs and Imatinib. By examining the available evidence and weighing the potential risks and benefits, medical professionals can make informed decisions regarding kidney transplantation for the specific patient population.

CASE PRESENTATION

In November 2019, a 63-year-old male patient developed end-stage kidney disease caused by diabetic nephropathy was referred to our hospital because he wanted living donor kidney transplantation from his sister as the donor. The patient's medical history was that he was diagnosed with CML in March 2003 at a hematology department of another hospital, started treatment with the tyrosine kinase inhibitor imatinib, and was in stable condition with Molecular Response (MR) in 2005, and continued imatinib treatment until he came to our hospital. At that time of his outpatient visit, he strongly preferred kidney transplantation in the choice of Renal Replacement Therapy (RRT) with his nephrologist and had not yet undergone hemodialysis. Based on the pre-transplant examination results, we determined that the patient was eligible for living donor kidney transplantation because his disease had been stable for more than over 15 years with imatinib treatment, and his general condition was good

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despite hypertension and type 2 Diabetes Mellitus (DM). In July 2020, he received his first kidney transplant from a 53-year-old living donor who was his sister (blood type match, serum creatinine (s-Cr) 0.58 mg/dL, eGFR 86.5 mL/min/1.73 m^2, HLA-A, -B, -DR-mismatch: 1-1-1).

A 64-year-old male recipient underwent ABO-compatible kidney transplantation in July 2020. This patient received a triple-drug immunosuppressive protocol (Tacrolimus (TAC), Mycophenolate Mofetil (MMF), and Methylprednisolone (MP)). In this patient, imatinib for CML was discontinued from the time of renal transplantation after careful consideration with the hematologist because of Deep Molecular Remission (DMR) of the Major Molecular Response (MMR) over 15 years prior to renal transplantation, while the interaction between immunosuppressive drugs and imatinib may make it difficult to regulate immunosuppressive drugs. Currently, the follow-up period after the kidney transplantation is 35 months. The most recent BCR-ABL1 monitoring showed that a profound molecular response persisted even without imatinib treatment (Table 1). Thus, this patient continues to maintain Treatment-Free Remission (TFR) status without imatinib for 35 months after renal transplantation. The post-transplant course was uneventful, with no delayed graft function, episodes of acute rejection, or surgical or infectious complications, and the renal allograft is currently functioning well. Furthermore, this patient was successfully transplanted with a transplanted kidney and is alive and well with no CML recurrence.

Table 1: Hematological and chemical laboratory data after kidney transplantation.

Year/Month	2020/ Mar	2020/ Jul	2020/ Aug	2020/ Sep	2020/ Oct	2020/ Nov	2020/ Dec	2021/ Jan	2021/ Mar	2021/ Jun	2021/ Sep	2021/ Dec	2022/ Mar	2022/ Jun	2022/ Sep	2022/ Dec	2023/ Mar	2023/ Jun
Months after stating imatinib	204	208	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Months after stating transplantation	-	0	1	2	3	4	5	6	8	11	14	17	20	23	26	29	32	35
Hematologic response																		
White blood cell count (3.3-8.6 ×10^9/L)	-	5.9	14.7	6.8	6.8	7.7	6.7	7.5	7.5	8.3	8.6	8.7	8	8	8.6	8.6	9.2	9.2
Neutrophils (38-74%)	-	67.4	73.9		69.1	68.1	69.4	67.7	69.1	70	71.6	68.6	70.6	71	72	71.5	71.6	70.9
Hemoglobin (13.7-16.8 g/dl)	-	11.4	11	10	12	13.1	13.3	13.3	13.9	13.6	13.9	14.4	14	13.9	14.3	14.3	13.9	14.4
Platelets (15.8-34.8 × 10^4/L)	-	15.3	13.9	17.8	19.9	22	21.8	23.6	23.7	21.1	21.9	23.6	21.6	19.7	20.7	22.1	20.2	20.4
Cytogenetic response																		
Molecular response	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]	MR4.5	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]	MR[5]
BCR-ABL IS (%) in peripheral blood	0.0008	0.0008	0.0007	0	0	0	0.0008	0	0	0.001	0.0026	0	0	0	0	0	0	0
Renal allograft function	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum Creatine (mg/dL)	4.46	5.31	1.08	1.07	1.26	1.17	1.27	1.31	1.48	1.31	1.26	1.35	1.17	1.19	1.17	1.16	1.05	1.17
eGFR (ml/min per 1.73 m^2)	11.5	9.5	51.2	54.9	45.9	49.8	45.3	43.8	38.3	43.8	45.7	42.2	49.3	48.4	49.3	50	55.3	49.3
Immunosuppression																		
Tacrolimus trough level (ng/mL)	-	12.3	9	8.5	8.9	7.1	7.6	7.1	6.4	8.7	5.8	6.9	7.1	6.3	8.8	6.8	5.7	4.7
Mycophenolate mofetil (mg/d)	-	1500	1500	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Methylprednisolone (mg/d)	-	20	16	12	8	6	4	4	2	2	2	2	2	2	2	2	2	2

RESULTS AND DISCUSSION

CML is a tumor of hematopoietic stem cells caused by the Ph chromosome. The Ph chromosome is a chromosomal aberration caused by a translocation of chromosomes 9 and 22 (t (9;22)), which results in the fusion of BCR on chromosome 22 and ABL on chromosome 9 to form BCR-ABL. ABL, a tyrosine kinase, forms a chimeric protein with the BCR, resulting in high proliferative activity and causing leukemogenesis. CML used to be a disease with a very poor prognosis, with a 2–3-year course, a chronic phase, a transition phase, and then an acute transformation leading to death. However, since the introduction of imatinib, a Tyrosine Kinase Inhibitor (TKI), in 2001, the prognosis has improved remarkably, and imatinib is now widely used as the first-line treatment for CML. Currently, TKIs have dramatically changed the survival of CML patients. CML is now managed as a chronic disease requiring long-term treatment and close molecular monitoring. It has been shown that in a substantial number of patients who have achieved a stable DMR.

On the other hand, currently, kidney transplantation is absolutely contraindicated for patients with Chronic Renal Failure (CRF) with active malignancy. Immunosuppressed kidney transplant recipients are also at higher risk of carcinogenesis than healthy individuals. However hematologic malignancies are very rare, except for malignant lymphoma encompassing Post-Transplant Lymphoid Hyperplasia (PTLD). Against this background, it is debatable whether renal transplantation can be safely performed in patients with a history of CML in remission. In reality, however, CML that develops after kidney transplantation is a very rare disease, with only a few dozen cases reported worldwide. On the other hand, the use of TKI therapy in CML patients with stable DMR is a promising approach to the management of this disease. CML is currently managed as a chronic disease requiring long-term treatment and close molecular monitoring. A significant number of patients who achieve stable DMR have been shown to be able to safely discontinue TKI therapy without loss of response [1-3].TFR with achievement of DMR has recently emerged as a new goal for CML treatment [1-3].

In July 2020, this case received his first kidney transplant from his sister. Immunosuppressive drug administration is essential in kidney transplantation. Imatinib should be used with caution in transplant patients because, as a CYP3A4 inhibitor, imatinib increases blood levels of Calcineurin Inhibitors (CNIs) such as TAC. There are few reports on the use of imatinib in kidney transplant patients, and the actual interaction between immunosuppressive therapy and imatinib is unknown [4-7]. Therefore, in the present case, imatinib for CML was carefully considered with the hematologist for two reasons: the patient had DMR for more than 15 years prior to kidney transplantation, and the interaction between immunosuppressive agents and imatinib may lead to difficulty in modulating immunosuppressive agents, resulting in acute rejection and infection, and finally, imatinib was discontinued at the time of kidney transplantation. For safe discontinuation of TKI therapy, the NCCN Guidelines for CML (2019 Ver. 1) states that, outside of clinical trials, discontinuation of TKI therapy appears safe in selected CML patients [1,2,8,9]. Furthermore, imatinib can be safely discontinued in patients with CMR sustained for more than 2 years [10]. The indication for TFR is patients in the first chronic phase with typical BCR-ABL transcripts who have been on TKI therapy for at least 5 years and have sustained DMR; Molecular Response 4.5 (MR4.5) for 2 years, etc [3]. Sustained DMR, on the other hand, must be demonstrated on at least 4 international reporting scale quantitative Polymerase Chain Reaction (PCR) tests, separated by at least 3 months, in the immediate prior 2 years [3]. In our case, as shown in Table 1, quantitative PCR testing confirmed that BCR-ABL had disappeared at least 2 years prior to renal transplantation, leading to a diagnosis of long-standing persistent DMR [11]. Furthermore, it is recommended that molecular monitoring be performed indefinitely after kidney transplantation, including monthly for the first 6 months, every 2 to 3 months from months 7 to 12, and every 3 months for the second year.

Currently, this patient continues to maintain TFR status without imatinib for 35 months after kidney transplantation. The posttransplant course was uneventful, with no delayed graft function, acute rejection episode, or surgical or infectious complications having occurred. The kidney allograft function is excellent at present. Tacrolimus trough values could be adjusted as usual without imatinib administration. He currently maintains good transplant kidney function and TFR status with a BCR-ABL fusion gene that has disappeared.

CONCLUSION

In conclusion, this result suggests that CML with long-lasting DMR on imatinib therapy can be considered an inactive malignancy and therefore a relative indication for kidney transplantation. Currently, kidney transplantation is absolutely contraindicated for patients with Chronic Renal Failure (CRF) with active malignancy. However, there is controversy as to whether kidney transplantation can be safely performed in patients with a history of Chronic Myeloid Leukemia (CML) in remission. Furthermore, it is recommended that molecular monitoring be performed indefinitely after kidney transplantation, including monthly for the first 6 months, every 2 to 3 months from months 7 to 12, and every 3 months for the second year.

DISCLOSURE STATEMENT

None declared.

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