Treatment of metastatic transitional cell carcinoma following renal transplantation

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■ Renal transplantation was performed in a patient with a history of surgical excision for localized transitional cell carcinoma. The graft functioned well; however, metastatic transitional cell carcinoma developed following transplantation. The patient was treated sequentially with CISCA (*cis*platin, Cytoxan [cyclophosphamide], and Adriamycin [doxorubicin hydrochloride]) and M-VAC (*m*ethotrexate, *v*inblastine, Adriamycin, and *c*isplatin) with no alteration in maintenance immunosuppression. Full-dose chemotherapy was well tolerated, with no impairment of renal function, and a demonstrable reduction in tumor burden was achieved. The patient ultimately died of metastatic disease but enjoyed an excellent quality of life throughout the post-transplant period.

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THE TREATMENT options for patients with cancer and end-stage renal disease are controversial. After excision of a localized malignancy in patients at high risk for metastasis, 12 to 24 months of dialysis have been recommended before renal transplantation.[1] If metastasis occurs after transplantation, the role of nephrotoxic chemotherapy is unclear. We report the first case of metastatic transitional cell carcinoma treated with nephrotoxic chemotherapy following renal transplantation.

CASE REPORT

A 39-year-old woman presented with irritative voiding symptoms in January 1978. Diffuse carcinoma in situ of the bladder was identified. She was treated with radiation therapy (4,000 rad [40 Gy]) via an intravesical radium catheter. Carcinoma in situ recurred, and in 1979, she underwent a radical cystectomy and construction of an ileal conduit. A pathologic study revealed focal severe dysplasia of the urothelium but no definite carcinoma. In December 1981, cytologic studies of the urine showed recurrence that was localized to the right kidney. In February 1982, a right nephroureterectomy was performed; pathologic study revealed a T1 N0 M0 Grade III transitional cell carcinoma of the renal pelvis.

Urine cytologic studies were again positive in November 1984, and positive findings persisted throughout six subsequent courses of mitomycin C instilled via her ileal loop. Despite these positive cytologic findings, a loopogram and intravenous pyelogram disclosed normal findings in February 1985. An evaluation of metastasis was done with a computed-tomographic (CT) scan of the abdomen and pelvis, chest radiograph, and bone scan. All of these tests were normal. After a long discussion with the patient, it was decided to

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proceed with a left nephroureterectomy, subsequent dialysis, and renal transplantation one year later if metastatic disease did not develop. In March 1985, a left nephroureterectomy was performed. Pathologic study revealed T3 N1 M0 Grade III transitional cell carcinoma of the left renal pelvis.

The patient started hemodialysis at a rate of three times a week. She tolerated dialysis poorly, experiencing numerous bouts of nausea, vomiting, hypertension, and congestive heart failure. Peritoneal dialysis was not possible due to adhesions from multiple prior abdominal operations. In October 1985, the patient believed that her life was miserable on dialysis, and she did not want to wait for a cadaveric transplant. There were no available family donors other than her husband, who emphatically requested that he be considered for a living unrelated transplant. The patient and her husband had the same red blood cell group, and a lymphocytotoxic crossmatch test was negative. The patient was restudied with a CT scan of the abdomen and pelvis, chest radiograph, and bone scan; none showed metastatic disease.

In November 1985, a spousal renal transplant was performed; the kidney was placed in the existing ileal conduit. Medication for the patient's maintenance immunosuppression consisted of cyclosporine and prednisone, which were gradually tapered to dosages of 10 mg/kg/day and 10 mg per day, respectively. Her allograft functioned immediately, and she was discharged two weeks postoperatively with a serum creatinine level of 1.0 mg/100 mL. There were no episodes of rejection following transplantation.

In late January 1986, the patient complained of back pain. A CT scan of her abdomen and pelvis revealed enlarged periaortic nodes. A chest radiograph showed multiple pulmonary metastases. In February 1986, intravenous administration of full-dose CISCA was started, consisting of *cis*platin (75 mg/m^2), Cytoxan (cyclophosphamide) (500 mg/m^2), and Adriamycin (doxorubicin hydrochloride) (60 mg/m^2). She tolerated this well, but yeast overgrowth developed and was treated with amphotericin B. There was no change in her renal function. Maintenance immunosuppression was not altered. In March 1986, a chest radiograph and CT scan of the abdomen revealed a partial response to the chemotherapy. She then received another course of CISCA in March 1986 along with 30 Gy of radiation to the para-aortic area. Her disease stabilized.

In July 1986, new metastatic pulmonary lesions developed, and the patient was given full-dose M-VAC, consisting of *m*ethotrexate (30 mg), *v*inblastine (5 mg), Adriamycin (doxorubicin hydrochloride) (40 mg), and *cis*platin (70 mg/m^2). She received two courses of M-VAC (one in August 1986 and one in November 1986), resulting in a symptomatic, but no objective, response. Leukopenia was noted after each course of treatment and resolved spontaneously. During treatments, there was no change in maintenance immunosuppression, and renal function remained stable with a serum creatinine level of 1.0 mg/100 mL. The patient enjoyed an excellent quality of life during her entire post-transplant period. In December 1986, she died of metastatic transitional cell carcinoma.

DISCUSSION

The timing of renal transplantation in patients with a prior treated malignancy is controversial. Penn[1,2] has reported a 48% recurrence rate in patients undergoing transplantation within 12 months of treatment for localized malignancy. This rate decreased to 20% for patients waiting 12 to 24 months, with no recurrence developing after a wait of more than 48 months. These observations applied not only to renal neoplasms but to other types of malignancies as well. Based on these data, the general recommendation has been to wait at least 12 to 24 months after complete tumor excision, in order to allow time for the patients at high risk for metastasis to be identified.[1–7] In our patient, early transplantation was prompted by her poor tolerance of dialysis and poor quality of life, and was performed eight months after her last treatment for neoplasm. Due to the emphatic desire of her husband to donate a kidney and the lack of any other family donors, a spousal transplant was performed. The possible increased risk of developing metastatic disease while on immunosuppressive therapy was carefully explained to the patient. In the event that metastatic disease did occur, it was hoped that the patient would be able to tolerate systemic chemotherapy. The patient and her husband understood this and elected to proceed with a transplant.

Despite the fact that metastases were absent on pre-transplant evaluation, a tumor developed two months after transplantation. The development of de novo post-transplant malignancies induced by immunosuppression is well described in the literature. There have been reports suggesting that immunosuppression may also facilitate spread of pre-existing malignancies, but this concept remains controversial.[6–8] Our patient was at high risk for tumor recurrence, and the role of immunosuppression in accelerating the appearance of metastases is unclear.

When metastases developed after transplantation,

our patient was treated initially with full-dose CISCA and then with full-dose M-VAC. Multiple chemotherapeutic agents have been used to treat metastatic cancer after solid organ transplantation, primarily in patients receiving liver allografts for fibrolamellar hepatoma, with only anecdotal reports of long-term patient survival.[8–11] The use of chemotherapy to treat recurrent urothelial malignancy following transplantation has not been reported previously.

Cisplatin-based multi-drug regimens have been effective against metastatic transitional cell carcinoma.[12] The dose-limiting factor is the nephrotoxicity of cisplatin. Cisplatin has been used occasionally for patients on dialysis but at much lower and less adequate dosages.[13] With a well-functioning renal allograft, our patient was able to tolerate full-dose chemotherapy and a partial tumor response was achieved. Maintenance immunosuppression was not altered, there was no impairment of allograft function, and leukopenic episodes were well tolerated.

Most importantly, the patient experienced an excellent quality of life throughout her entire post-transplant period. Although Mandel and Kjellstrand[9] have reported post-transplant malignancies regressing with discontinuation of immunosuppressive medications, this concept is questionable and carries the risk of allograft loss from rejection. Our patient was unwilling to consider this option due to the poor quality of life she had experienced on dialysis.

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