

## Renal Transplantation Under Cyclophosphamide

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**B**EGINNING 15 mo ago, at the University of Colorado, the alkylating agent, cyclophosphamide (Cytoxan), has been given an extensive clinical trial in the treatment of whole organ recipients both early and late after transplantation. This communication will deal only with those cases of renal homotransplantation in which cyclophosphamide was used from the outset. The late substitution of cyclophosphamide for azathioprine has been thoroughly described elsewhere.<sup>1</sup>

### THERAPEUTIC PROTOCOLS

Cyclophosphamide was given as part of a triple drug program that also included prednisone and horse ALG. When related donors were available, all three agents were started several days in advance of operation (Fig. 1) but for cadaveric cases (Fig. 2) treatment was started on the day of operation. The ALG was confined to the first 2-4 mo postoperatively. Prednisone was adjusted as needed to control rejection (Fig. 1-3). The donor-recipient combinations were not selected on the basis of a good HL-A match, and in most instances this kind of typing information was not even taken into consideration.

The precise details of treatment during the early postoperative period have been

published<sup>1</sup> but it would be good to review some significant points. First, the cyclophosphamide was used in almost exactly the same way as has been customary with azathioprine, designing doses on a day-to-day basis according to the white counts, and with a conscious effort to avoid leukopenia. Second, the correct doses on a milligram per kilogram body weight basis were somewhat smaller than would have been anticipated had azathioprine rather than cyclophosphamide been used. Third, attention was paid to the possibility of specific toxicity of cyclophosphamide, including alopecia, anorexia, and hemorrhagic cystitis. At the doses used, alopecia was the only complication noted frequently, at about a 4% incidence.

Finally, a change was, as a rule, eventually made from cyclophosphamide to maintenance therapy with azathioprine (Fig. 3). At the earliest, this transition was at about 1 mo posttransplantation and at the latest after more than 1 yr. Lately, the switch has been carried out arbitrarily after 2 mo or before this time if doses of cyclophosphamide of at least 0.5 mg/kg have not been tolerated without producing leukopenia. The rationale for the successive use of these two cytotoxic agents lies in the dissimilarity of their properties (Fig. 4). Cyclophosphamide is an alkylating agent said to exert its effect at the premitotic (or G<sub>2</sub>) phase of the cell cycle of immunocytes. In contrast, azathioprine is a purine analog that is an inhibitor of DNA synthesis. The objective has been to eliminate more effectively the clone of sensitized and replicating cells responding to the homograft antigens. The consecutive use of drugs in order to achieve "longitudinal" synergism in contrast to the "horizontal" syner-

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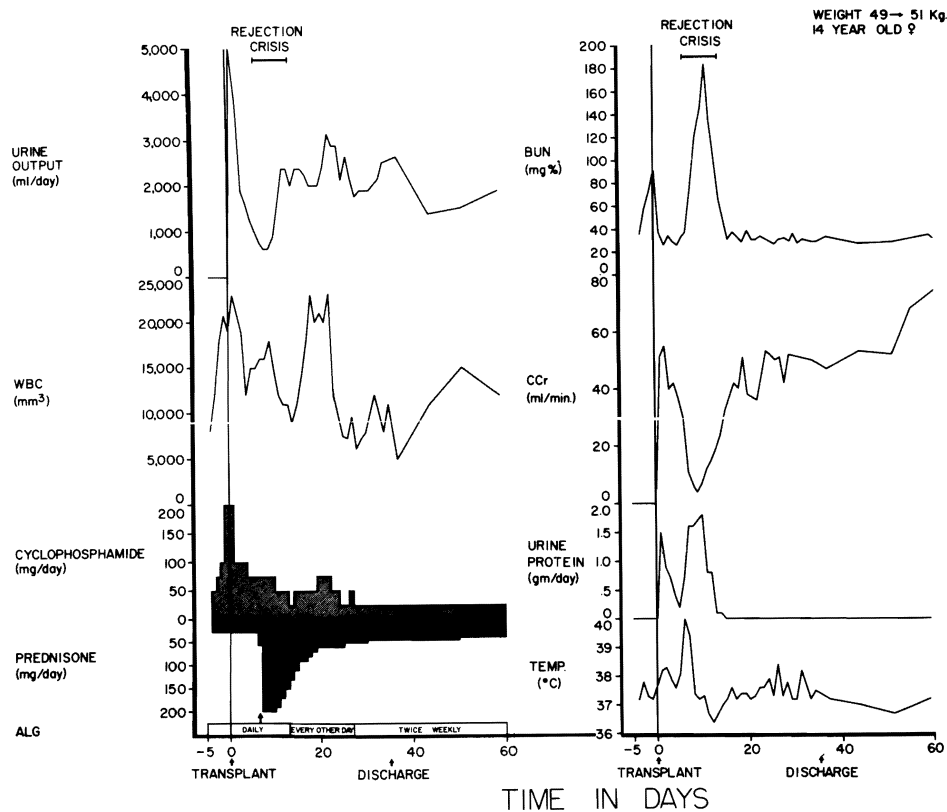


Fig. 1. The first 60 days after the transplantation of a kidney from a mother to her 14-year old daughter. The rejection crisis after 1 wk was the most severe observed in the intra-familial cyclophosphamide series, with the exception of two hyperacute rejections. However, it was reversed easily and completely. Note that leukopenia was never produced by the daily doses of cyclophosphamide that were usually between 0.5 to 1 mg/kg/day. Arrow, 625 mg methyl prednisolone intravenously. (By permission of Surg. Gynec. Obstet. 133:981, 1971.

gism of simultaneously administered agents has become common in cancer chemotherapy.

### RESULTS

Follow-ups of 3–15 mo are now available. Thirty-nine recipients of related kidneys (Table 1) have survived at the rate of 90%; kidney survival has been 32 of 39 (82%). All the living patients now have adequate function of their consanguineous transplants.

In recipients of nonrelated kidneys, survival is 28 of 36 (78%). These 36 patients

were given 40 kidneys (Table 2) and the kidney survival is 73%. It is necessary in evaluating these results to appreciate that 17 of the recipients were entered into the series by virtue of their retransplantation for the second to fifth times. Kidney survival was only 10 of 17 (59%) in these notoriously bad risk patients with their high incidence of presensitization and other complications (Table 2). Moreover, six of the deaths were in this group. In contrast, there was a 10% patient mortality (two deaths in recipients undergoing cadaveric transplantation for the first time) and a

Fig. 2. The uncomplicated early course of a 20-yr-old recipient of a cadaveric kidney. Therapy with cyclophosphamide, prednisone, and ALG was instituted on the day of operation. (By permission of Lancet 2:70, 1971).

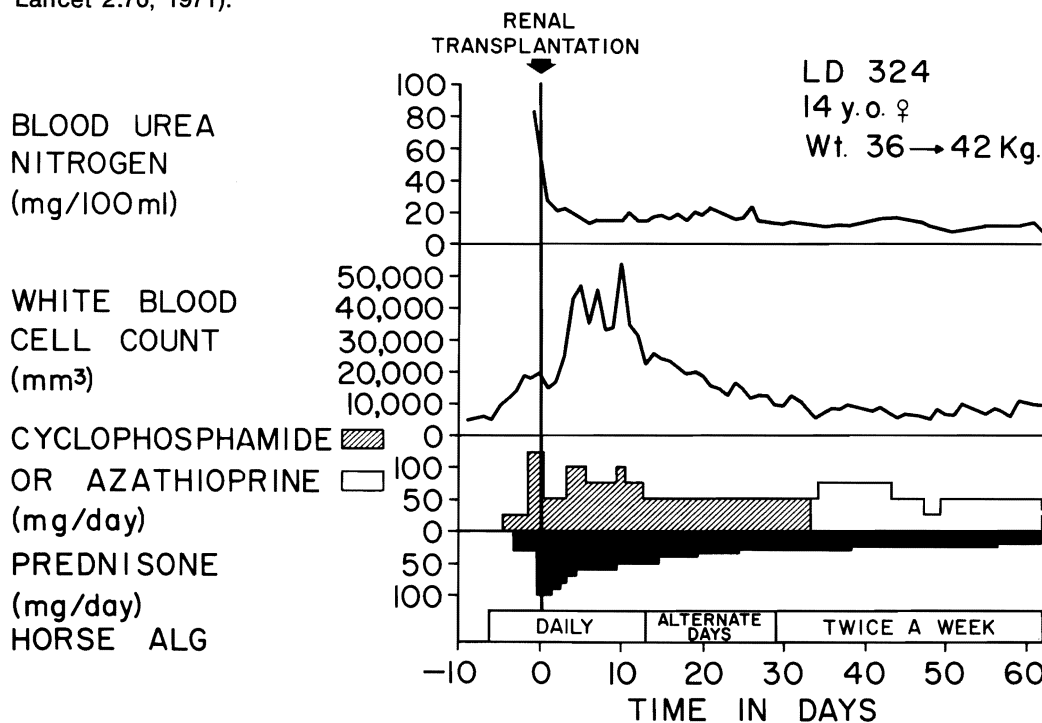
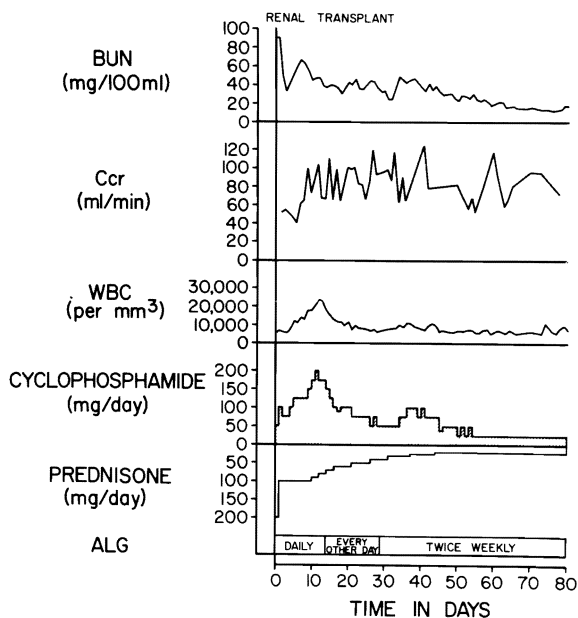


Fig. 3. The first 2 mo posttransplantation of a 14-yr-old recipient of a paternal homograft. Her initial immunosuppressive therapy was with cyclophosphamide, prednisone, and horse ALG. The daily doses of cyclophosphamide were always greater than 1.3 mg/kg/day and were given for the first 33 days postoperatively. The switch to azathioprine was then made because of a progressive decline in the white blood cell count. The recipient has never had a rejection episode and her renal function continues to be normal 5 mo posttransplantation.

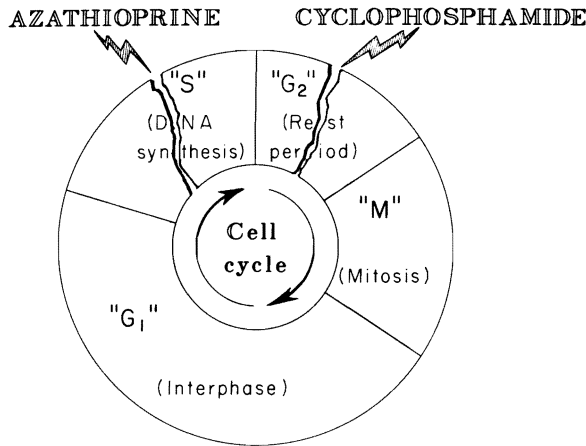


Fig. 4. The different sites of action during the cell cycle of the cytotoxic drugs, azathioprine, and cyclophosphamide. Rapidly replicating lymphoid cells are presumably preferentially susceptible to destruction by either agent.

present kidney survival of 19 of 23 (83%).

**SUMMARY**

In these studies, cyclophosphamide has been shown to be a good enough immunosuppressive agent to replace azathioprine during the early postoperative period and

Table 1. Cyclophosphamide: Related Cases\*

	Follow-ups of 3-15 Mo		
	Original No.	Remaining No.	Per Cent
Recipients	39	35	90
Kidneys	39	32	82

\*22 Siblings, 14 parents, 1 aunt, 1 cousin, and 1 grandmother.

Table 2. Cyclophosphamide: 40 Cadaveric Kidneys in 36 Recipients Follow-ups of 3-15 Months

	No.	Functioning
Primary grafts*	23	19 (83%)
Repeat grafts†	17	10 (59%)
Total	40	29 (73%)

\*2 Deaths  
†6 Deaths

for as long as 1 yr with satisfactory results. Eventually, cyclophosphamide was replaced by azathioprine in most cases. The consecutive use of these chemically and pharmacologically dissimilar drugs may have advantages in terms of longitudinal synergism.

**REFERENCES**

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