The Effect of Local Irradiation in Prevention and Reversal of Acute Rejection of Transplanted Kidney with High-dose Steroid Pulse*

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From 1979 to 1984, 39 local allograft irradiations were given to 29 patients: 10 irradiations were administered for prevention and 29 for reversal of acute rejection of transplanted kidney. Three doses of 150 cGy every other day were combined with high-dose of methylprednisolone pulse (1 gm/day) for 3 days. For prevention of acute rejection, local irradiation was delivered on the days 1, 3, and 5 after the transplantation, and for reversal, irradiation started after the diagnosis of acute rejection.

Eight out of 10 patients irradiated for prevention had acute allograft rejection, and, what is more, there was no surviving graft at 15 months after transplantation.

Reversal of acute rejection was achieved in 71%. When the pre-irradiation level of serum creatinine was below 5.5 mg%, the reversal rate was 93%, but above 5.5 mg % the reversal rate was only 17% ($p < 0.01$). Reirradiation after failure was not successful. Among 15 reversed patients, 7 (47%) had subsequent rejection (s). The functional graft survivals at 6 month, 1, 2, and 3 year were 70%, 65%, 54%, and 54%, respectively. Therapeutic irradiation resulted in better graft survival when serum creatinine was below 5.5 mg% ($p < 0.001$) or when irradiation started within 15 days after the diagnosis of acute rejection ($p < 0.001$).

Key words: Local allograft irradiation, Kidney transplantation.

INTRODUCTION

Renal transplantation has become the accepted therapy for the end-stage renal failure since 1954. For successful function of allograft, rejection is the limiting factor. Major antigens of HLA histocompatibility gene complex play crucial roles. In addition, minor antigens—ABO blood groups, a newly defined endothelial-monocyte system—are recognized to be involved in. Selection of donors by careful HLA matching and manipulation of the recipient's immune system with immunosuppressive agents has helped the graft survival increase markedly. However, rejection has been observed in 10 to 15% after the matched HLA renal grafts.[1] In order to prevent and reverse the immunologic rejection, corticoseroids (prednisone, methylprednisolone), azathioprine, antilymphocytic globuline, irradiation (total body irradiation, total lymphoid irradiation, extracorporeal irradiation of blood, local allograft irradiation), cyclosporine, and combined methods have been used.[2,3,4,5,6,7,8,9] As for the effectiveness of local allograft irradiation, many studies were for it,[10,11,12] while others were against it.[13,14,15]

To determine the effectiveness of local irradiation to kidney allografts, we analyzed the results of local allograft irradiation which were given for prevention or reversal of acute rejection. Prophylactic efficacy, reversal rate, functional graft survival, and influencing factors are discussed.

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MATERIALS AND METHODS

From May 1979 to December 1981, 10 allografts were locally irradiated for prevention of acute rejection, and from January 1980 to August 1984, 29 allografts were irradiated for reversal in the Department of Therapeutic Radiology, Seoul National University Hospital. Among the 29 irradiations for reversal, 2 were radiated after failure of previous prophylactic irradiation, 3 were treated twice, 1 three times, and 1 four times. Therefore total of 29 patients were irradiated. The ages of patients ranged from 14 to 58 years, and 25 of them were males. The most of donors were the relatives of the patients (Table 1).

Diagnosis of acute rejection was made by the usual clinical criteria which included fever, weight gain, swelling of the grafted kidney, oliguria, increase in serum creatinine and BUN, and decrease of creatinine clearance. Radionuclide renal scan or ultrasonography was performed to differentiate acute rejection from obstructive renal failure, and biopsy was performed in some cases. Acute rejection was combined with acute tubular necrosis in 2 patients in whom the allografts were from cadavers.

Prednisone and azathioprine (Imuran) were used as conventional systemic immunosuppressive agents. Initial prednisone dose was 150 mg/day and reduced to the maintenance dose of 30—40 mg/day. Imuran was given 4—5 mg/kg/day and its maintenance dose was 2—3 mg/kg/day being adjusted with the leucocyte count. Methylprednisolone (Solumedrol) was administered with pulse injections of 1 gm/day on 0, 1, and 2 days after transplantation or after acute rejection.

Prophylctic irradiation was given on the post-transplantation days 1, 3, and 5, 150 cGy/day. Therapeutic irradiation of the same dose was given on 0 to several days after Solumedrol pulse injections. Irradiation was delivered with AP PA parallel opposed ports, and its field size ranged 8 × 11 cm to 10 × 15 cm.

Evaluation criteria were as follows. Reversal was defined as improvement to the normal range in serum creatinine within 2 months after completion of irradiation. Partial reversal, as improvement over 50% in serum creatinine within 2 months with or without increasing tendency toward initial level. No reversal, as persistent increase or stable level of serum creatinine. Effective functional graft survival was defined as maintenance of normal kidney function from the day after completion of irradiation to the onset of irreversed deterioration or to the time of patient's death of all cause or to the time of lost to follow up. Life table method and logrank test were used in survival analysis and chi-square test was used in comparison with reversal rates.[16] Overall follow-up rate was 83% (Table 2)

RESULTS

1. Rejection Prevention

Of the 10 patients who received prophylactic irradiation, 8 had 1 to 3 times of acute rejection and 2 other died of pulmonary infection without rejection within 10 months after transplantation. Anti-rejection therapy included 2 reirradiation was delivered to 8 patients who suffered from rejection, but all the grafts ceased to survive by aforementioned criteria. The causes of death were renal failure in 3 patients, renal failure with infection in 3.

Table 1. Graft Distribution as to Donor and Matched HLA Antigens

Donor	Irradiation Aim		Total
	Prophylactic	Therapeutic	
Related	8	18	26
1Ag	3	4	7
2Ag	3	6	9
3Ag	2	5	7
4Ag	—	3	3
Unrelated	2	1	3
Cadaver	—	2	2
Total	10	21*	31

*2 grafts with subsequent rejection after prophylactic RT was included.

Table 2. Kidney Allograft Irradiation (1979—1984)

No. of Patients		Follow-up Period (Median) in Months
Prophylactic	10 (90%)	
Reversal Aim	19 (79%)	
Lost	4	4 — 55 (21)
Followed	25	1 — 59 (13)
Total	29 (83%)	

*Numbers in parentheses are follow-up rates.

removal of allograft in 1, and lost with chronic rejection in 1. Sixteen percent graft survival was observed at 1 year and 15 months survival was none. Therefore, prophylactic local aloograft irradiation immediately after transplantation was not successful.

2. Rejection Reversal

Of the 21 patients who received therapeutic irradition, reversal was achieved in 15 (71%), (Fig 1), partial reversal in 3, and no reversal in 3 which includes 1 patient who received irradiation at the third rejection. Analysis on the influencing variables to find the possible prognostic factors showed that pre-irradiation level of serum creatinine was the only affecting facotr (Table 3). In Table 3, 'yes' to the response to Solumedrol was defined as decrease in the level of serum creatinine of any degree after administration. Reversality did not depend upon the steroid response.

The second course of local irradiation was applied to 3 PR's and 1 NR, but reversal could not be obtained (Table 4). Subsequent irradiations resulted in similar patterns. Thus, if the reversal had not been obtained by the first course of irradiation to rejected allograft, further course of irradiation seemed to be of no benefit at all. Four allografts did not survived after reversal failure by the first course of irradiation.

Table 3. Factors Influencing Reversal

Factor	Reversal (%)	P Value
Rejection time		
after transplant		
within 30 day	8/13 (62)	> 0.05
after 30 day	7/ 8 (88)	
Donor		
Related	14/18 (78)	
1Ag	3/ 4 (75)	
2Ag	5/ 6 (83)	
3Ag	3/ 5 (60)	> 0.05
4Ag	3/ 3 (100)	
Unrelated	0/ 1 (—)	
Cadaver	1/ 2 (50)	
RT after		
rejection Dx		
within 15d	13/17 (76)	> 0.05
after 15d	2/ 4 (50)	
Pre-RT creatinine		
above 5.5mg%	1/ 6 (17)	< 0.01
below 5.5mg%	14/15 (93)	
Response to		
Solumedrol		
yes	3/ 4 (75)	> 0.05
no	12/17 (71)	

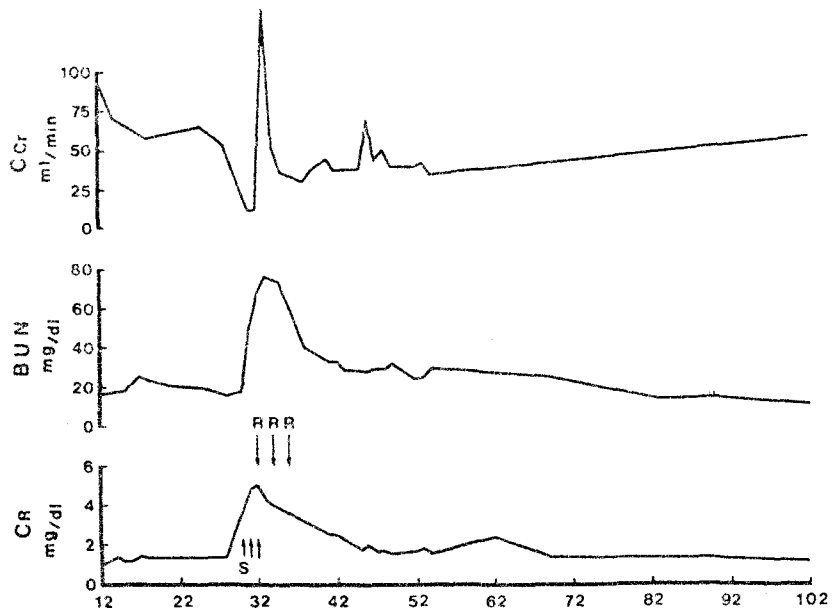

Fig. 1. Acute rejection developed on the 30th day after transplantation was reversed by local graft irradiation on days 32, 34, and 36 with 150 cGy/day. 'S' means pulse IV of Solumedrol 1 gm.

3. Subsequent Rejection

Of the 15 reversed patients, 7 (47%) had subsequent rejection once or twice. Two patients, who suffered from acute rejection despite prophylactic irradiation, died of uremia. One patient received second course of irradiation but failed to reverse and died of acute renal failure. Among 4 other patients who received conventional drug therapy, 2 had reversal and are still alive.

Table 4. Reversal Patterns of Repeated Irradiation

Course	Reversal	Partial Reversal	No. Reversal
1st RT	15	3	3
2nd RT	—	2	2*
3rd RT	—	1	1
4th RT	—	—	1

*1 case given 150 cGy only is included.

Table 5. Effective Functional Graft Survival

Condition	Graft Survival (%) 6M	1Y	2Y	3Y	P Value
Overall	70	65	54	54	
Pre-RT Level of serum creatinine					
below 5.5mg%	86	79	72	72	<0.001
above 5.5mg%	25	25	11	11	
Period*					
within 15d	85	80	75	75	<0.001
after 15d	44	29	—	—	
RT Response					
R	93	86	79	79	
PR	25	25	—	—	<0.001
NR	—				

*between the diagnosis of the rejection and irradiation.

4. Graft Survival

The functional graft survival at 1 and 2 years after treatment for acute rejection were 65% and 54%. Three main factors influencing the survival are tabulated in Table 5. Other factors such as interval of rejection after transplantation, numbers of matched HLA antigens, and response to Solumedrol did not influence the survival.

Longterm graft survival after rejection could be achieved with early irradiation, irradiation to the marginally damaged allograft, and when response to the irradiation was complete reversal. Seven grafts are still functioning well over 2 years after therapeutic irradiation

DISCUSSION

The rejection mechanism is known as follows. At the rejection site, small number of sensitized host lymphocytes release migration inhibitor factor and macrophage activation factor, and these factors induce the round cell infiltration and made non-sensitized cells involve in rejection. Donor specific cytotoxic T cells are concentrated first in the graft and appear in the circulation secondarily 4 to 5 days after grafting. Early in the rejection B cells and killer cells which are capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) also appear in the infiltrate in allograft. Later, antigen specific cytotoxic cells and Ig-secreting B cells are present in the infiltrate too[2, 11].

Local allograt irradiation seems to exert its effect by destroying lymphocyte or macrophage which might carry alloantigen to the host immunocyte thereby destroying cytotoxic T cells, killer cells, and B cells[17, 18]. And it is well known that by differential radiosensitivity in lymphocytes or even in T cells, suppressor T cells dominate and Helper/Suppressor ratio decrease after systemic or local irradiation[2, 5, 19]. Additional postulate of action mechanism of local irradiation is non-specific non-immunologic reduction of interstitial edema. This was derived from the report that increase in graft size with threatened rejection was promptly reduced in size after local irradiation and that small dose (200 cGy × 3 fractions) of local irradiation improved the renal function in dog kidney damaged by induced ischemia with renal artery clamping[20, 21].

Many animal experiments of local allograft irradiation showed prolongation of allogarft survival without systemic reaction. When local irradiation is the only immunosuppressive agent, significant effect was obtained with 6 doses of 150 cGy over 12 to 15 days in mongre dog. If the first dose was delayed until the second or third day after transplantation or doses below 150 to 200 cGy were used, benefit was not obtained[22]. Four doses of 150 cGy on days 1, 3, 5, and 7 after transplantation showed to be effective, and the same dose regimen was also effective in reversing the established rejection[23]. However a canine experiment showed that irradiation consistently prolongs the recovery period from acute tubular necrosis after tranplantation[11]. In rat, the effective dose to produce

pyknotic degeneration of 50% of lymph node cells is 150 cGy, and in man maximum lymphocyte depletion after total body irradiation occurs at 200 to 250 cGy[22]. So there are no controversy in dosage.

Therefore, according to the animal experiments, radiation appears to be effective as the sole immunosuppressant, but in clinical reports radiation was always combined with the conventional imunosuppressive drugs and so radiation effect was not clearly determined and evaluated. This is the basic difference between clinical and experimental application of local irradiation.

Levitt reported that 34% of patients were rejection free after 4 doses of 150 cGy every other day combined with immunosuppresive drugs, and the greater the number of repeated irradiation, the lesser the chance for success, and graft suvival at 2 years was 60% in living related grafts and 39% in cadaver grafts[10].

Godfrey and Salaman reported that no benefit was obtained by additional local allograft irradiation to the high-dose methylprednisolone thereapy in randomized clinical trials to treat the first acute rejection. Reversal of rejection within 4 weeks was better in irradiated group (58% vs 50%), but functional graft survival at 1 year was better in non-irradiated group (50% vs 26%)[13]. But in their trial, pre-treatment level of serum creatinine was higher in irradiated group and, what is more important, their data was not statistically analyzed. Pilepich et al, in their randomized trial, failed to demonstrate a beneficial effect of local graft irradiation when used in conjunction with high-dose steroids[14,15]. But, in their trial, repeated irradiation to the recurrent rejection was not analyzed separately.

But local allograft irradiation alone reversed the acute rejection successfully in patients having contraindication to systemic immunosuppressive agents due to established life-threatening infection[11]. And these were confirmed in recent report, which showed 4 reversal out of 6 patients who were unable to tolerate further systemic antirejection agents because of systemic infection and 21% graft survival at 1 year in patients who did not respond to high-dose steroid[12]. These reversed grafts would not have survived otherwise.

Previous report by one of authers analyzed clinical observations on ranal transplantation performed in our hospital. The report compiled 80 cases treated between August 1973 and June 1984 and the cases included all the cases of the present study except one. Thirty five percents (28/80) of patients had acute rejections 1 to 3 times and graft survival rates at 6 months, 1, and 2 years were 93%, 86%, and 80% respectively.[24] Of course survival in present report is inferior, but the survival of those grafts that already had acute rejection but achieved reversal after local irradiation coincides interestingly with that of the former report.

Though irradiation is clearly effective, conventional immunosuppressive drugs are still needed. So it is difficult to decide what portion of our result comes from the irradiation. Limiting factors of local irradiation for the effective reversal, in our result, requires early delivery of local irradiation after the diagnosis of acute rejection. In these days newly developed cyclosporine is more widely being used. But it is still necessary to clarify the role of the local alograft irradiation in combined regimen or as a single treatment in clinical trials using cyclosporine with or without local irradiation.

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=국문초록=

국소적 방사선조사의 신장이식후 거부반응에 대한 예방적 및 치료적 효과

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1979년부터 1984년까지 이식신에 대하여 39회의 국소적 방사선조사가 서울대학교병원 치료방사선과에서 시행되었다. 10회는 예방적으로, 29회는 치료적으로 시행되었고 전체 환자수는 29명이었다.

방사선조사는 1일 150 cGy로 격일간 450 cGy를 원칙으로 하였으며 methylprednisolone(Solumedrol)과 동시 병용되었다. 면역억제제로서 prednisone과 Imuran은 이식후 계속 투여되었다. 방사선조사 시기는 예방목적일 경우에는 이식수술후 1,3,5일에, 치료목적인 경우에는 거부반응의 진단후 어느정도 시간간격을 두고 시행되었는데, 간격은 개인차이가 있었다.

10예의 예방적조사를 받은 이식신의 8예가 추후 거부반응이 출현하였으며, 이식후 15개월후에 기능적 생존을 보인 예는 없어서 예방적조사 효과는 희의적이었다.

치료목적으로 처음 조사받은 21예의 거부반응 회복율은 71%였고, 방사선조사전 혈청 크레아티닌이 5.5 mg% 이하일 경우는 93%, 5.5 mg%이상일 경우는 17%였다($p<0.01$). 회복이 안된 경우 재차 방사선조사에 대한 효과는 초회효과보다 열등하였다.

거부반응이 회복된 경우에 47%가 재차 거부반응이 출현하였다.

거부반응에 대한 처음 방사선조사후 이식신의 기능적 생존율은 방사선조사후 6개월, 1년, 2년 및 3년에 각각 70%, 65%, 및 54%였고, 방사선조사전 혈청 크레아티닌 수준, 거부반응 진단후 방사선조사까지의 경과시간 및 방사선조사후의 반응등이 이식신의 기능적 생존에 유의한 영향을 미침을 알 수 있었다($p<0.001$).

따라서 방사선조사로 효과를 얻기 위하여는 거부반응으로 인한 이식신 파괴가 한계수준을 넘지 않는 범위내에서 시행함이 필요함을 알 수 있었다. 이 효과는 Solumedrol과 병용된 결과이므로 방사선조사의 상대적 기여도를 밝히는 것은 어려웠다.