AZATHIOPRINE INDUCED BONE MARROW SUPPRESSION IN LIVE RELATED RENAL ALLOGRAFT RECIPIENTS

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ABSTRACT

Over a follow-up period of 6 years, 4 out of 31 live related renal allograft recipients (12.9%) developed azathioprine induced bone marrow suppression. Presentation in 3 patients was with fever and 2 patients also had associated graft dysfunction. All patients had leucopenia, 2 patients in addition had anaemia and one patient had pancytopenia. Bone marrow suppression developed 9.6 months (3.5-16.0 months) following transplantation and recovery followed over a period of 30 (18-49 days) days after withdrawal of the drug. One patient succumbed during the phase of bicytopenia.

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KEY WORDS : Azathioprine; Bone marrow suppression; Kidney transplantation.

Introduction

Azathioprine (AZA) remains one of the most frequently used immunosuppressive drugs for live related renal allograft (LRR) recipients and has to be taken life long [1,2]. One of the most important and feared side effects of the drug is bone marrow suppression, reported in 14-35% of patients [1,3,4]. This usually recovers following withdrawal of the drug or reduction in dosage. Leucopenia is the commonest manifestation and is reported among 96% of those developing myelosuppression. Anaemia occurs in 60% and thrombocytopenia in 30% of these cases [4]. In developed countries, where immunosuppressive protocols incorporated a higher dosage of AZA, bone-marrow suppression was reported to occur early. This contrasts with countries like India, where this side effect reportedly occurs late and with a slower period of recovery [4]. This variation is probably related to the cumulative dose of the drug [5]. Infections remain the major risk during the phase of leucopenia. Presence of pancytopenia, graft dysfunction, severe leucopenia ($< 2000/\text{cumm}$), fever, and sepsis prognosticate a dismal outcome [4,6].

Material and Methods

Thirty one patients who received LRR between Jan 88 and Mar 94 were the subjects of the present study. All LRR recipients were monitored for haematological disturbances. Haemoglobin, total and differential leucocyte counts and platelet counts were estimated weekly during the first month, fortnightly till the third month and monthly thereafter. The following criteria were used for cytopenia :

Leucopenia $< 3000/\text{cumm}$

Hb drop $> 25\%$ from the previous level

and platelet count $< 100,000/\text{cumm}$

If any patient developed fever, routine haematological and biochemical parameters, blood and urine cultures, radiological investigations and other relevant tests were done. In patients with cytopenia, study of bone marrow aspirates was done. Other factors contributing to myelosuppression like administration of a myelotoxic drug or infections such as cytomegalovirus, hepatitis B virus were also looked for. If other incriminating factors were absent and the patient improved following withdrawal of AZA, the myelosuppression was considered to be due to this drug.

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Graft dysfunction was evaluated by serial blood urea, serum creatinine, ultrasonography, and graft biopsy.

Result

The male : female ratio was 29:2, mean age was 39.7 years (22-40 years). The mean follow up period was 18.3 months (4 months to 7 years). Four patients developed AZA induced bone marrow suppression (12.9%).

Following transplantation 23 patients were on triple drug regimen with AZA, cyclosporine A, and prednisolone. Seven patients were on a two drug protocol with cyclosporin and prednisolone while 1 patient was on AZA and prednisolone. By the end of one year, all patients were receiving AZA and prednisolone only.

Three patients presented with fever which persisted for a mean period of 7.6 days (5-11 days). All of them were given broad spectrum antibiotics (third generation cephalosporins/aminoglycosides and cloxacillin). Despite a diligent search for the offending organisms, none could be isolated in any of the cases.

In one of the patients, though IgM titres for cytomegalovirus remained high (> 50 units/mL), bone marrow recovered following withdrawal of AZA, hence cytomegalovirus was not considered to be the cause of bone marrow suppression.

All 4 patients with bone marrow suppression had leucopenia, 2 patients in addition had anaemia and one had thrombocytopenia (Table 1). The mean period of recovery following withdrawal of AZA was 30 days (18-49 days). One patient had a fatal outcome. This patient presented with fever and altered sensorium. He had leucopenia. De-

tailed evaluation including CSF study and CT scan did not give clue to the offending organism. While on broad spectrum antibiotics, the patient succumbed on 14th day of myelo-suppression.

Discussion

AZA is a nitroimidazole derivative of 6-mercaptopurine. The immunosuppressive potential of this drug was realized soon after its synthesis in 1961, and thereafter it became an accepted drug in immunosuppressive protocols following renal transplantation. The drug inhibits both DNA and RNA synthesis and recent studies indicate that the immunosuppressive action of this drug results predominantly from a block in the production of interleukin-2 [1,2].

Bone marrow suppression due to this drug is reported in 14-35% patients [3]. A recent study from India reported bone marrow suppression in 14.3% of their patients [4]. Three phases of AZA induced bone marrow suppression have been described : stage of megaloblastic erythropoiesis, stage of defective granulopoiesis, and stage of toxic panmyelopathy [7]. Pollock observed that all his patients who developed myelosuppression did so in the first 8 weeks of AZA exhibition with a mean period of 3.6 weeks [8]. However, a report from India observed immunosuppression after an average exposure of 16.3 months [4]. This variation could be the result of the different dosage schedules followed and by ethnic variations. Most western workers find recovery within 2 weeks of stoppage of the drug while an Indian study found bone marrow recovery in a mean of 2.6 months [4]. We observed recovery over a period of 30 days. This variation is possibly due to differences

TABLE 1
Azathioprine induced bone marrow suppression

Patient	Immunosuppressive protocol	Time Gap (AZA exposure-cytopenia)	Hb level (g/dL)	TLC (in mm ³)	Platelet count (mm ³)	Bone marrow findings	Total dose of AZA (g)	Final outcome
1	CyA+AZA+Pred	3½ months	5.2	1100	> 100000	Bi-cytopenia	10.5	Died, Day 13
2	AZA+Pred	13 months	6.0	800	70000	Pan-cytopenia	50.6	Recovery, Day 22
3	AZA+Pred	6 months	> 10	2500	> 100000	Leucopenia	22.5	Recovery, Day 18
4	CyA+AZA+Pred	16 months	4.8	700	> 100000	Bi-cytopenia	37.2	Recovery, Day 49

CyA - Cyclosporine A; AZA - Azathioprine; Pred - Prednisolone

in the cumulative dose of AZA.

To forestall myelosuppression, it is important to identify the patients who are likely to develop the complication. A suggested method is to give a bolus of hydrocortisone intravenously. Patients who fail to mount a leucocytic response following this are vulnerable to develop bone marrow suppression later [9].

Infections are the major concern during immunosuppression and are responsible for the bulk of morbidity and mortality during the leucopenic phase. Common Gram negative organisms responsible for infections in these patients are *E. coli*, *Serratia* and *Pseudomonas* while *Staph. aureus* is the commonest Gram positive isolate [10].

AZA should be the prime suspect responsible for leucopenia in LRRRA recipients and the drug needs to be stopped or its dosage reduced. The importance of periodic haematological assessment in these patients cannot be overemphasised.

REFERENCES

1. Ramos EL, Tilney NL, Ravenscraft MD. Clinical aspects of renal transplantation. In: Brenner and Rector, editors. The Kidney, 3rd ed. Philadelphia: WB Saunders & Co 1991: 2361-407.
2. Walker RG, d'Apice AJ. Azathioprine and steroids. In: Morris PJ, editor. Kidney Transplantation. Philadelphia: 1988.
3. Hasslein HC, Pierce JC, Lee HM, Hume DM. Leucopenia and azathioprine management in renal homotransplantation. Surgery 1972; 71: 598-604.
4. Sakhuja V, Kalra OP, Verma S, Chugh KS. Azathioprine induced bone marrow suppression. Abstract 4D 0108, Asia Pacific Congress of Nephrology 1992.
5. Monto HO, Dummer JS. Infections in transplant recipients. In: Mandell GL, Bennet JE, Dolini R, editors. Principles and practice of infectious diseases. 4th ed. New York: Churchill Livingstone 1995; 2709-16.
6. Anderson RJ, Schafer LA, Olin DB, Eickhaff TC. Infectious risk factors in immunosuppressed host. Am J Med 1973; 54: 453-9.
7. McGrath, Ibels LS, Raik E et al. Erythroid toxicity of azathioprine. Quart J Med (New series) 1975; 173: 57-63.
8. Pollock R, Nishikawa RA, Mozes MF, Jonasson O. Azathioprine induced leucopenia - clinical significance in renal transplantation. J Surg Res 1980; 29: 258-63.
9. Fisher KA, Hill JL, Mahajan SK, Stuart FP. Prediction of azathioprine intolerance in renal transplant patients. Lancet 1976; i: 828-30.
10. Myerowitz RL, Medeiros AA, O'Brien TF. Bacterial infections in renal homotransplant recipients. Am J Med 1972; 53: 308-14.