Effect of Myleran Therapy in Multitransfused Thalassemic Children

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Thalassemia syndrome is an inherited disorder affecting either alpha or beta chain synthesis(1,2). Allogenic bone marrow transplantation offers cure(3) but is feasible in nearly 30% of cases. However, only few lucky thalassemic children have undergone bone marrow transplantation because of its prohibitive cost. It has been observed that an

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increase in fetal hemoglobin (gamma chains) synthesis can ameliorate the severity of thalassemia (4-6). Various chemotherapeutic agents such as 5-azacitidine, hydroxyurea and myleran have been used to stimulate gamma chain synthesis to increase fetal hemoglobin level. In the present study myleran has been used in three courses at 15 days interval to evaluate its efficacy in increasing the hemoglobin and fetal hemoglobin levels.

Material and Methods

Thirteen thalassemic children (seven boys and six girls) under regular blood transfusion therapy in the Hematology Department, between the ages of 3-6 years, were selected. Parents of these children had consented for the study after knowing well the possible benefits and side effects of drug therapy. Diagnosis of beta thalassemia in these children had been established, between 4-11 months of age based upon their clinical features, hemoglobin level, blood morphology, fetal hemoglobin and hemoglobin A2 levels on the index case and family studies. Various clinical and laboratory parameters were recorded on a predesigned proforma for the study. Children who were positive for HIV infection or with impairment of renal functions and increase in transaminases level by more than two fold, that of normal levels were excluded.

Amount of packed cell transfusion per month (ml/kg body weight), during the study period and following six months of study period was kept same for each case, as over the preceding six months, to evaluate, the effect of myleran therapy. These children were administered myleran in single dose of 0.15 mg/Kg/day for period of 15 days. Three such courses of drug therapy were administered at 15 days apart. Hemoglobin level, total and differential counts, reticulocyte count and hemoglobin F level were determined prior to each course and on the 7th and 15th day of drug therapy. Subsequently all these parameters were evaluated prior to each blood transfusion.

Results

No consistent pattern of either rise or fall in hemoglobin level was observed following three courses of myleran therapy (Table I). However, a rise in hemoglobin level of over 0.5 g/dl was seen following first and second course in 9 of 13 (69.2%) cases. Changes in hemoglobin levels were analyzed using block analysis and analysis of variance and the rise in hemoglobin level was statistically insignificant.

Similarly, no consistent pattern of change in fetal hemoglobin was observed with each course (Table II). Rise in mean HbF level varied between 31-70%. However, when the data was subjected to Friedman Ranksum analysis, the rise in fetal hemoglobin was not

<table>
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<tr>
<th>TABLE I- Change in Hemoglobin with Myleran.</th>
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<tr>
<td>Change in hemoglobin (g/dl)</td>
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<tr>
<td>------------------------------</td>
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<tr>
<td>Course I</td>
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<tr>
<td>Rise&gt;0.5</td>
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<tr>
<td>No change (-0.5 - +0.5)</td>
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<td>Fall &gt;0.5</td>
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statistically significant. No consistent pattern was seen with corrected reticulocyte count. However, 61.5% of patients had a rise in corrected reticulocyte count which was statistically insignificant.

The mean hemoglobin levels over the preceding six months, during therapy period and following six month period were compared. Eleven of 13 (84.6%) children had a rise in hemoglobin level during therapy period and seven of thirteen (53.8%) children continued to have higher mean hemoglobin level following therapy. Although the rise in hemoglobin level was statistically insignificant, a definite trend of rise in hemoglobin level was observed. No adverse effects were documented. The total leucocyte count and platelet count continued to remain within normal levels. Hepatic and renal functions were normal during and after therapy.

Discussion

Over the last one decade, efforts have been made to prevent or reverse the globin gene switch in an attempt to maintain the expression of the fetal globin gene. Studies on 5-azacytidine were discontinued because of its mutagenic and carcinogenic effects(7). Subsequently other agents have been evaluated with variable success(8,9). In these reports, blood transfusions were withheld and children continued to suffer from chronic hypoxia during the study. However, in the present study blood transfusions were not withheld on ethical grounds and the children continued to get blood transfusion at the same rate (ml/kg/month) as over the preceding six months.

A rise in mean hemoglobin level in 11 (84.6%) children during therapy and in 7 of 13 (53.8%) children for six months after therapy was observed. The rise in hemoglobin level in these patients varied between 0.2 to 2.0 g/dl. It was less as compared with other studies(8,9). In contrast to hemoglobin level, the rise in fetal hemoglobin was transient and, its level decreased within 15 days of therapy. The rise in fetal hemoglobin was also less in comparison to other studies(8,9) except in one case in which the fetal hemoglobin level increased from 6.9% to 42.4% following the first course and reached to it's peak level of 45.5% following the second course and remained higher than 9% for six months. A rise in Hb F levels is considered to be a function of the basal level(10).
minimal rise as the initial fetal hemoglobin level was low in our cases. Another possible factors for poor rise in Hb F level was poor erythropoietic activity, which was evident by low corrected reticulocyte count.

Erythropoietic activity was being continuously suppressed by regular blood transfusion therapy in the present study in contrast to other studies in which transfusion therapy was withheld(8,9). Myleran in higher dose for a longer period could also explain the better response(9). Thus the rise in fetal hemoglobin and hemoglobin level appear to be dependent on the dose and duration of therapy. Further studies are essential to determine the optimal dose and therapy schedules to have the maximum beneficial effect with least toxicity.

REFERENCES


