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CASE REPORT

SPLENIC INFARCTS FOLLOWING TREATMENT WITH FILGRASTIM – AN UNUSUAL COMPLICATION

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Abstract:
We report a case of acute lymphoblastic leukemia (ALL) with baseline splenomegaly (pretreatment) on chemotherapy having splenic problems while on treatment with filgrastim for chemotherapy related neutropenia. We suggest strict adherence to cautious prescription of filgrastim with '5 microgram per kilogram per day' dosage for a maximum of 14 days per month with an extra vigilance for patients with pretreatment splenomegaly. We have documented the decreased level of antithrombin III with filgrastim related adverse effect, which is open for further confirmation of association.
Keywords: lymphoblastic leukemia, chemotherapy ,case report

INTRODUCTION:

Splenic problems are known complications of filgrastim therapy. Filgrastim therapy is often unavoidable supportive therapy in chemotherapy related neutropenia . Physicians often come across patients having baseline splenomegaly who are candidates for chemotherapy and subsequent filgrastim therapy. We discuss one of such situations which shows the importance of optimum dose of filgrastim therapy in such cases.

CASE REPORT

A fifteen year old male having 34 kg weight presented with breathlessness & fatigue since one month. He had recent history of multiple blood transfusions. There was no history of bleeding. He was conscious, oriented and his vital parameters were normal. On general examination, he was found to have severe palor. There was no icterus, lymphadenopathy, cyanosis, oedema or clubbing. He had bone tenderness. On systemic examination, cardiovascular system, central nervous system and respiratory system were normal but per abdominally he revealed moderate splenomegaly i.e. 5 cm palpable below costal margin. He had no past or family history of any medical illness.

Complete blood count(CBC) on first presentation showed, haemoglobin (Hb)- 4.4 g/dL, total leucocyte count (TLC)-23000/µL with 28 % blasts, platelet count (PLC)- 1000/µL, with normal liver (LFT) & renal(RFT) function tests. On bone marrow examination the morphologic picture was hypercellular marrow, 89 % blasts, high nucleus/cytoplasmic ratio, altered myeloid/ erythroid ratio, lack of megakaryocytes, morphologically suggesting acute lymphoblastic leukemia(ALL). On immunophenotyping(IPT), the blasts mainly expressed B lymphoid markers CD79a (92 %), CD 19 (99%), CD22 (33%) and Tdt (88%) along with CD34 (79%), HLADR (98%) and CD 10 (99%). Co- expression of CD34/CD22 was 23 %, CD 34/CD 19 was 77 % CD 10/CD22 was 33 % & CD 10/19 was 99 %. He was diagnosed to have pre-pre B cell ALL. Philadelphia chromosome test was negative by fluroscent insitu hybridisation(FISH) method. Ultrasonography showed splenomegaly with spleen size of 8 centimetre.

Initially he was started on first phase of induction(I-1) of MCP 841 protocol of ALL therapy with daunorubicin, vincristin, steroids, L–asparginase and intrathecal methotrexate. Leucocyte counts gradually started falling. While receiving chemotherapy, 8th day of first phase of induction (I-1,day8) was awaited when the patient had epistaxis and hospitalisation. He was detected to have fever, pansinusitis, pleural effusion, hemoperitonium, gross ascitis and hepatosplenomegaly. At this time spleen size was 16 cm. During investigations ,stool culture detected E.coli. Biochemistry revealed pancytopenia with grade-4 neutropenia (absolute neutrophil count i.e . ANC < 500 /µL), deranged liver function ,with hypoalbuminemia. This episode lasted for 11 days. we treated this patient with sensitive antibiotics and filgrastim (300µg daily for 11 days).[1] Chemotherapy was restarted further. Injections of L –asparginase were started on 22nd day of induction. Again he had abdominal pain and loose motions, hence we suspected pancreatitis but serum amylase level was normal. He recovered from this episode with conservative treatment and tolerated further chemotherapy till the end of I-1. Post I-1 bone marrow was in remission. Cerebrospinal fluid cytology was negative for malignant cells.

Second phase of induction(I-2) was delayed for 15 days due to one more episode of gastroenteritis which required antibiotic treatment. Imaging revealed spleen size 13 cm and two splenic infarcts (62 × 24× 53 mm ;35 × 27× 50mm) and few mesenteric nodes. Sickling test was negative and osmotic fragility was normal. I-2 was started and followed as per protocol. 15th day of second phase of inducton(I-2,day 15) was delayed for 10 days due to 6-mercaptopurine induced grade-4 neutropenia and treated with filgrastim (150 µg for 6 days). I-2 was completed after recovery of counts.

Reinduction(RI) also deayed for 5 days due to grade 4 neutropenia. Reinduction started on TLC -2000/µL. Reinduction day 8 (RI,day 8) was delayed for 5 days due to persistant leucopenia and grade 4 neutropenia. Again this was treated with (filgrastim 300µg for 4 days). Reinduction day 22 (RI,day 22) was similarly delayed for 10 days due to grade 4 neutropenia. Eventually reinduction completed.

Consolidation (CDN) chemotherapy treatment started and filgrastim (300µg for 7 days) was supported due to expected delayed count recovery. Patient admitted on consolidation day 10 (CDN day 10) with febrile neutropenia (which progressed further to grade-4) and deranged LFT. He was treated with antibiotics and filgrastim (300µg for 5 more days). In this presentation Hb was 2.3g/dL , TLC was 5500µ/L, PLC - 71000µ/L. With total bilirubin 2.75mg/dL(indirect 2.21

mg/dL) and international normalized ratio (INR) 3.25. Imaging revealed Splenomegaly of 18 cm with multiple infarcts.

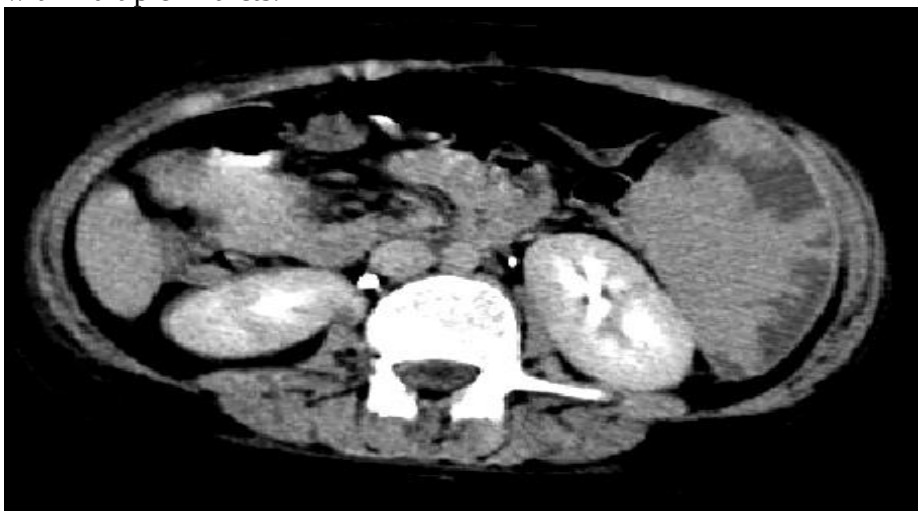

Figure 1:CT scan image of this patient showing slenomegaly with multiple splenic infarcts.

Here we ruled out L–asparginase as cause of splenic infarctions by reviewing the temporal profile of the events which started before receiving L-asparginase. After stabilisation we did work up for thrombophilia profile which was normal except mild decrease in antithrombin III level. (INR -1.33, activated partial thromboplastin time i.e APTT-32.2 second for patient /32.1 second for control, lupus anticoagulant was absent, factor V 1691 –normal, factor II 20210-normal, MTHFR 677–normal, protein C-normal, protein S – normal, antithrombin III–70 % the reference interval being 80 – 120). Thus we concluded in this case that the cause for recurrent splenic problems was attributable to filgrastim. The exact mechanism of splenic enlargement, infarction and rupture is not described in available literature but may be correlated to extramedullary hematopoesis. We have documented mild decrease in antithrombin III level, which needs to be carefully confirmed in similar other settings.

This patient reverted from critical status with antibiotics and supportive treatment. We excluded filgrastim from treatment prescription of this patient. Further this patient is at present pursuing maintenance regimen smoothly for last 7 months. Splenomegaly persisted till this moment but the intercurrent events of abdominal pain related to recurrent splenic infarctions did not recur.

DISCUSSION

Overall most commonly observed adverse effect of filgrastim is mild-to-moderate bone pain after repeated administration and local skin reactions at the site of injection. Those with sickle cell disorders may suffer sickle cell crisis after receiving filgrastim therapy. Other adverse effects comprise spleen rupture, serious allergic reactions, alveolar hemorrhage, acute respiratory distress syndrome (ARDS), and hemoptysis.[2-3]

Splenomegaly is frequently observed at pretreatment baseline in severe neutropenia patients and is commonly noticed early in the course of treatment with filgrastim. The clinical trials monitored spleen size by physical examination and one phase III trial by imaging studies. Palpable splenomegaly was documented at baseline in 15% of study patients and in 30% of

patients on filgrastim. Computed tomography or magnetic resonance imaging showed a median increase in spleen volume of 38% over the first 5 months of filgrastim treatment (range, 2% to 148%). Spleen volume then tended to plateau around 18 months and around 2.5 years it decreased toward pretreatment values. Registry data confirmed the common finding of pretreatment splenomegaly, reported at baseline in 18% of patients with congenital neutropenia. During the first year of filgrastim therapy, the prevalence increased to 38.2% and remained near this level (27% o 45%) through 10 years of therapy. Splenomegaly have been correlated with the underlying disease , its progression, severe infection, or may be associated with leukemic transformation.[4]

According to Cal Optima Injectable Medication Guideline & NCCN guidelines for Filgrastim, the recommended dose of filgrastim for cancer patients receiving chemotherapy is 5 µg/kg/day & maximum number of doses per month for filgrastim are 14 doses per month.[5-6]

CONCLUSIONS

From this case we could be able make many inferences. First , the prescription of filgrastim in pediatric and adolescent patients should be given after weighing the risk and benefits in each individual patient because we have less data of filgrastim use in this age group in acute lymphoblastic leukemia. Second, filgrastim should be prescribed cautiously using '5 microgram per kilogram per day' schedule and even the maximum duration of treatment for neutropenia should be restricted upto maximum 14 days. Third, to prevent filgrastim related adverse effects , extra vigilance is required in presence of baseline splenomegaly. Fourth, the mechanism of filgrastim related adverse effects ,which is not explained in literature could be related to decrease in antithrombin III level and needs further confirmation.

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