Granulocyte-macrophage colony-stimulating factors (G-CSF) Treatment for Severe Congenital Neutropenia (SCN)

Introduction

- **Definitions**

- **Neutropenia** absolute neutrophil count (ANC) <1500/microL

- **Leukopenia** refers to a low WBC that may be due to lymphopenia as well as neutropenia

- **Granulocytopenia** refers to a reduced number of granulocytes (neutrophils, eosinophils, and basophils).

- **Agranulocytosis**: the absence of granulocytes, but the term is often used to indicate severe neutropenia (ANC <200/microL).

Introduction

- Congenital neutropenia

Any neutropenia present at or near birth, would include transient immune neutropenias as well as inherited causes.

Introduction

Diseases or syndromes of congenital neutropenia

SEVERE CONGENITAL NEUTROPENIA

- The availability of G-CSF (filgrastim, lenograstim) therapy has dramatically changed management, resulting in a significant reduction in infections and improvement in the quality of life [6,7,45-47]

SEVERE CONGENITAL NEUTROPENIA

One hundred twenty-three patients with recurrent infections and severe chronic neutropenia (absolute neutrophil count<0.5 x 10(9)/L) due to these diseases were enrolled in this multicenter phase III trial. They were randomized to either immediately beginning recombinant human granulocyte colony-stimulating factor (filgrastim) (3.45 to 11.50 micrograms/kg/d, subcutaneously) or entering a 4-month observation period followed by filgrastim administration. Blood neutrophil counts, bone marrow (BM) cell histology, and incidence and duration of infection-related events were monitored. Of the 123 patients enrolled, 120 received filgrastim. On therapy, 108 patients had a median absolute neutrophil count of>or = 1.5 x 10(9)/L. Examination of BM aspirates showed increased proportions of maturing neutrophils. Infection-related events were significantly decreased (P<.05) with approximately 50% reduction in the incidence and duration of infection-related events and almost 70% reduction in duration of antibiotic use. [45]

SEVERE CONGENITAL NEUTROPENIA

- with most patients responding to a dose between 3 and 10 mcg/kg per day and fewer than 5 percent of patients not responding to 100 mcg/kg per day [48,49]. All responding patients have had reduced infections and a markedly improved quality of life

SEVERE CONGENITAL NEUTROPENIA

- Data on more than 600 patients with CN collected by the Severe Chronic Neutropenia International Registry (SCNIR) demonstrate that, regardless of the particular CN subtype, more than 95% of these patients respond to recombinant human (rHu)G-CSF with ANCs that can be maintained above 1.0 x 10(9)/L. [49]

SEVERE CONGENITAL NEUTROPENIA

- Patients involved in the phase I/II/III trials were continued on long-term maintenance treatment, and an international registry was established that had enrolled 374 patients with SCN through 2001 [6,40,50]. The median dose of filgrastim required to maintain an ANC greater than 1500/microL in patients with SCN was 5.6 mcg/kg per day

SEVERE CONGENITAL NEUTROPENIA

- In phase I-III studies in SCN patients, treatment with recombinant human granulocyte colony stimulating factor (r-metHuG-CSF; Filgrastim) resulted in a rise in the absolute neutrophil counts (ANC) to above 1.0 x 10(9)/L associated with a reduction in bacterial infections. Long-term treatment with filgrastim up to 8 years demonstrate a sustained ANC response, a significant reduction of the need for intravenous antibiotics and a dramatic improvement in the quality of life. [50]

SEVERE CONGENITAL NEUTROPENIA

- Tác dụng phụ
- Two complications of concern are the development of malignancy and a high frequency of osteopenia and osteoporosis.

We updated a prospective study of 374 SCN patients on long-term G-CSF enrolled in the Severe Chronic Neutropenia International Registry. Long-term, the annual risk of MDS/AML attained a plateau (2.3%/year after 10 years).[40]

SEVERE CONGENITAL NEUTROPENIA

- Tác dụng phụ
- Of the 30 patients investigated, 15 had evidence of osteopenia/osteoporosis observed on spine radiographs (n = 5), on Q-CT/DXA (n = 1/n = 1), or on radiographs and Q-CT (n = 8). In 13 of the 30 patients, only a lateral radiograph of the lumbar spine was available, 5 of 13 showing either increased kyphosis and wedging of the vertebrae or compression fractures of the vertebral bodies, indicating severe establishedosteoporosis. In eight patients, the findings of the spinal radiographs were normal. In nine patients, spinal radiographs were taken before r-metHuG-CSF treatment. Osteoporotic vertebral deformation (n = 3) or reduced bone mass (n = 3) was seen in six of these nine patients. The levels of serum biochemical markers of bone metabolism were all within normal ranges except for mild elevation of the serum alkaline phosphatase level. The degree of spinal bone mineral loss did not correlate with dose and duration of r-metHuG-CSF treatment or with the age or sex of the patients. [52]

SEVERE CONGENITAL NEUTROPENIA

- Thất bại điều trị
- patients who failed to achieve an ANC >2188/microL (2.188 x 10 /L) in spite of G-CSF doses above 8 mcg/kg/day were at elevated risk of sepsis, death, and MDS/AML.
- For those requiring more than 8 mcg/kg/day G-CSF, there was an 18 percent (95% CI 7-28%) sepsis risk and 34 percent (95% CI 21-47%) for MDS/AML [40].
- We updated a prospective study of 374 SCN patients on long-term G-CSF enrolled in the Severe Chronic Neutropenia International Registry. Long-term, the annual risk of MDS/AML attained a plateau (2.3%/year after 10 years) [40]