QUESTION 20

In adult Philadelphia-chromosome-positive chronic myeloid leukaemia (in chronic phase), treatment with which of the following agents is associated with the greatest likelihood of achieving a complete cytogenetic response?

A. Hydroxyurea
B. Radioactive phosphorus
C. Interferon
D. Cytosine arabinoside
E. Imatinib

MYELOPROLIFERATIVE DISORDERS

- Heterogeneous group of disorders characterised by cellular proliferation of one or more haematological cell lines in the peripheral blood, distinct from acute leukaemia
  - Consists of 4 diseases:
    o CML
    o Polycythaemia rubra vera
    o Essential thrombocytosis
    o Myelofibrosis
- Clonal origin
- Common attribute is acquired activating mutation of gene coding for tyrosine kinases
- In CML, tyrosine kinase activity of bcr-abl hybrid gene is increased
- In PRV, ET and MF mutations occur in JAK2 gene

CML

- Increased proliferation of granulocytic cell line without loss of capacity to differentiate
- Peripheral blood shows increased number of granulocytes and their immature precursors including occasional blast cells

Pathophysiology

- Characterised by cytogenetic aberration \( \rightarrow \) reciprocal translocation between long arms of chm 22 and 9 t(9,22)
- Results in shortening of chm 22 = Philadelphia chromosome
- This translocation relocates an oncogene (abl) from long arm of chm 9 to long arm of chm 22 in BCR region
- Resulting bcr-abl fusion gene encodes protein with strong tyrosine kinase activity
- Autophosphorylation and constitutive activation of tyrosine kinase

Epidemiology

- Typically affects middle aged (40s to 50s)
- M>F
Phases of Disease

1) Chronic Phase (3-5yrs)
   a. Splenomegaly
   b. Leukocytosis
   c. Few symptoms
   d. Easily controlled with medications

2) Accelerated Phase
   a. Occurs few months before blast crisis
   b. Survival 1 to 1.5 yrs
   c. Counts more difficult to control with medications
   d. Diagnosis with one or more of:
      i. Blast cells (10 to 19% of peripheral WBCs or nucleated BM cells)
      ii. Peripheral basophils (>20%)
      iii. persistent thrombocytopenia (<100) or thrombocytosis (>1000)
      iv. Increasing splenomegaly or leukocytosis unresponsive to Rx
      v. Cytogenetic evidence of clonal evolution

3) Blast Crisis
   a. Similar to acute leukaemia
   b. Survival 3-6 months
   c. Marked increase in BM or peripheral blast count (>20%)
   d. Large foci or clusters of blasts in BMBx
   e. Maybe soft tissue/skin leukaemic infiltrates, extramedullary blast proliferation
   f. Symptoms due to anaemia, thrombocytopenia, basophilia, rapidly enlarging spleen
   g. Failure of medications to control leukocytosis and splenomegaly
   h. 2/3 – myeloid blasts, 1/3 – lymphoid blasts
   i. Usually further chromosomal abnormalities found at this time

Clinical Manifestations

- Insidious
- Often asymptomatic at diagnosis
- Enlarged spleen +/- liver
- Fatigue, weight loss, low grade fever, night sweats $\rightarrow$ hypermetabolic symptoms
- Hyperviscosity $\rightarrow$ visual disturbances
- Gout

Pathology

- WCC 20-60, predominantly neutrophils
- Neutrophils have decreased apoptosis $\rightarrow$ long-lived cells $\rightarrow$ reduced enzymes/granules $\rightarrow$ low score on leukocyte alkaline phosphatase staining
- Mild basophilia and eosinophilia is common
- Early myeloid cells (eg: myeloblasts, myelocytes, metamyelocytes) and nucleated RBCs in peripheral blood and in BM – this differentiates CML from AML in which there is a “leukaemic gap”
- Mild to moderate anaemia usually normochromic, normocytic
- Platelets can be low, normal or sometimes increased
- Increased urate

**Bone Marrow**

- Hypercellular
- Expansion of myeloid line (neutrophils, eosinophils, basophils)
- Megakaryocytes prominent
- Mild fibrosis in reticulin stain
- Philadelphia chromosome (also often seen in peripheral blood)
- Additional chromosomal abnormalities may be found as patients enter blast crisis phase

**Treatment**

- Aims of treatment:
  - Haematological remission (normalisation of peripheral blood counts, no immature cells, no clinical signs of disease)
  - Cytogenetic remission (complete = no Ph+ cells; partial = 1-35% Ph+ cells; minor = 35-95% Ph+ cells)
  - Molecular remission (no brc-abl TK)
- Imatinib (Gleevec) competitively binds to ATP receptor of BCR-ABL TK → inhibits TK activity in cells with brc-abl → inhibits proliferation and induces apoptosis
- Side effects = oedema, muscle cramps, nausea, diarrhoea, abnormal LFTs, rash (porphyria)
- Degree of suppression of BCR-ABL TK predicts freedom from progression
- Other TK inhibitors are dasatinib and nilotinib
- Imatinib resistance can occur by 3 mechanisms:
  - Amplification and over expression of BCR-ABL
  - Mutations of BCR-ABL kinase domain
  - Drug influx-efflux-OCT-1 expression
- If resistance occurs can increase dose (variable response) or change to other TK inhibitor
- Other treatment options include hydroxyurea (haematological remission but cytogenetic/molecular remission rare), IFN and BM transplant

**Prognosis**

- Much better since imatinib became available ?estimated life expectancy
- Poorer prognosis associated with advanced age, more blasts, more basophils, larger spleen, more eosinophils and low platelets

Answer: E