**Hematology 1st lecture by Prof. BaHakim**

Introduction

* In order to get cancer, one must have two insults. The first is in the germ cells (genetic), and the second is environmental (including in-utero insults).
* The proto-ocogene must first be activated to oncogene for cancer expression. E.g. a patient that is genetically predisposed to HCC won’t be affected until he gets hepatitis and cirrhosis. Nasopharyngeal carcinoma after EBV. But some get these infections and still do not get cancer due to the presence of tumor suppression gene (p53), each person has two copies one from each parent (one is enough).
* The lack of this gene (p53) is responsible for 50% of inherited cancers. P53 is the guardian to all cells. It resembles a recessive inheritance meaning that one allele is enough to protect against cancer. During duplication, it gives the signal to other genes to repair every error occurring in the DNA. If the process (error) is not overwhelming, the error can be easily repaired. If it is too late for repair, the cells go into programmed cell death (apoptosis). This is the protective mechanism against inherited types of cancers.
* BBB of p53 deletion! Breast (≤50), brain and bone morrow (blood) cancers are typical p53 deletion cancers. If the patient still has the p53 and have activated oncogene, they will still get the cancer.
* EBV with translocation of segment (8;14), will lead to aggressive type NHL.

Leukemia

* T(9;22) -Philadelphia gene- is a very bad prognostic factor and has a poor response to therapy in ALL in children, whereas it’s a good prognostic factor in CML in adults. Hyperdiploid has a good prognosis to ALL.
* ALL is the commonest cancer in pediatrics age group. It selects children. Pre B cell (before it reaches B cell maturation) leukemia is the commonest subtype of ALL and its usually silent. It has the best prognosis and 95% can get treated after one year of chemotherapy.
* You need to do flow-cytometry to know the immunological type of ALL. B.M aspiration will show high blast count and this is confirmatory.
* Chronic leukemia is very rare (1%) in pediatrics, its usually Philadelphia negative and it carries the worst prognosis.
* T cell leukemia accounts for 10-15% of ALL. It presents as an emergency with acute lymphadenopathy, splenomegaly, anemia and WBC > 50,000 (non- specific finding), and commonly affects children more than 10 years. Unlike pre-B cell, which has a predilection to the brain. It has aggressive course and a bad prognosis.
* Down syndrome increases the risk of leukemia (30x normal population). If it affected them in the neonatal period (2-3 months) its most likely AML, while if they’re affected by the age of 2-3 years then it’s most likely ALL. AML has a better prognosis than ALL in Down.
* Chromosomal fragility increases the risk of leukemia. Examples:

1. Fanconi syndrome

* AR mostly, 1-2% are x-linked.
* Presentation:

hyper-pigmentation (commonest presentation 70-90%), Short stature, small eyes and ears, *aplastic anemia*, 25% are normal phenotypically but they will discover it in U/S by horse-shoe kidney.

* They develop AML and die from it unless they get stem cell transplantation.
* To confirm the diagnosis you need to do chromosomal testing (BM aspiration is not enough).

1. Bloom syndrome

* Photosensitivity with severe rash to the sun, with mental retardation and short stature.
* They develop ALL or lymphoma. One third of lymphomas will convert to leukemia before coming to the hospital.

1. Ataxia Telangiectasia syndrome

* Present with telangiectasia and vesicles all over their body.
* They are at increased risk to develop lymphomas. They have fragmented chromosomes (unrepaired errors).

1. Hypo-gammaglobinemia or A-gammaglobinemia patients are at increased risk to ALL.
2. Shwachman–Diamond syndrome (SDS)

* Rare congenital disorder characterized by exocrine pancreatic insufficiency, diarrhea, bone marrow dysfunction (congenital neutropenia), skeletal abnormalities and short stature.
* Neurofibramatosis type 1: can present with fever. if they got an abdominal mass think of neuroblastoma of the kidney, and they can present with bilateral neurosensory deafness, think of acoustic neuroma.
* Facial hemihypertrophy and absent iris (with no familial history of aniridia) and came with abdominal mass, think of Wilms tumor.
  + If the patient doesn’t have a family history of aniridia, must follow up every 6 months by examination and U/S of kidney, and every year by CT to check for Wilm’s tumor due to the high association.
* Leukemia may present with the following:

1. Pyrexia of unknown origin (the commonest presentation): 70% will be due to an infectious disease, 20% autoimmune causes, 1-5% malignancy (the commonest in Pediatric is ALL affecting 1:300,00 while neuroblastoma affects 1:106).
2. Bone pain: it’s always serious unlike abdominal pain (where 80% of the causes are psychological), whenever present admit the patient and do further investigations to find the cause even if the child was healthy.
3. Infections such as pneumonia or urinary tract infections (UTI). Commonest presentation of ALL is generalized bone pain.
4. Inflammatory Arthritis with effusion: might be a juvenile arthritis or brucellosis, if its due to leukemia when you do a tap you’ll find a high numbers of blasts. Arthritis due to autoimmune disorders are 4 times more common than it is in ALL.
5. Neutropenia: you must admit the patient and start him on IV antibiotics because the most common cause of death in cancer patients is infection.

* Cancer is the second most common cause of death in children after accidents but the most common disease causing death.
* Any fever in leukemia must be considered as an infection until proven other wise.
* Causes of death in cancer patients: 80% infection, 15% bleeding from thrombocytopenia, 5% cancer itself.
* Physical examination is non-specific.
* Hepatosplenomegaly, petechial hemorrhage and fever are seen in DIC ,or leukemia, we differentiate by CBC.
* CBC in leukemia will show: low HB, WBC are abnormal it reflects the burden of the disease (very high or very low) or normal, platelets are low (the commonest (more than WBC abnormality).
* T(4;11) and infection is an extremely bad because it is associated with WBC > 100,000.
* Investigations:
* Investigate for infections and autoimmune disorders, and if it fails go for BM aspirate, which will be full of blasts.

1. CBC.
2. B.M sample and check for blast invasion. Blasts will also be seen in the liver, spleen causing splenomegaly and lymph nodes.
3. Flow cytometry to know the subtype (T-cell, pre-B cell, B cell).
4. Genetic analysis to know the abnormality.

Complications:

1. Infection: viral infection is the most common, but we still treat for bacterial infections by multiple broad-spectrum antibiotics covering gram positive, and gram-negative aerobes and anaerobes (flagyl, clindamycin) because they have no neutrophils. We treat them for 48 hours; it is most likely it is bacterial if they recover.
2. Bleeding: it’s due to thrombocytopenia, intracranial bleeding is the most common (highest risk).

* Therefore, we must correct the thrombocytopenia by platelet transfusion if the platelet count is less than 30,000 or if its 70,000 in a febrile child till the platelets reach 100,000. If a patient has a platelet count of 40,000 with bone marrow failure, must always check PT, PTT, and D-Dimer before transfusion of platelets to rule out DIC that could lead to death in a few hours. You check the D-dimer, PT, APTT; if they’re high, then suspect DIC and must treat by FFP not only platelets transfusion.
* In platelet transfusion you have to put the child’s surface area into consideration e.g. 1 bag/1m2 increases the platelets by 10,000, if the patient came with a platelet count of 30,000 you must give him 7 units to raise it to 100,000.

1. Tumor lysis syndrome: this will result in high uric acid levels, and it must be corrected to prevent renal failure by hydrating the patient giving him allopurinol which will competitively inhibits xanthine oxidase inhibiting uric acid synthesis; you also give NaHCO3 to alkalize the urine to prevent crystallization (which is the commonest cause of hyperurecemia). Also correct any electrolyte imbalance.
2. Anemia: it must be corrected gradually by blood transfusion depending on level of hematocrit (aim 36) to prevent fluid overload and heart failure. Patients can have cardiomegaly due to the chronic anemia. Doses of blood transfusion must be spread over 24 hours and lasix should be given in between. Hb:Ht is 1:3.

* Treatment:

1. Stabilize the patient and correct all the complications first.
2. Treat leukemia: The treatment of choice is steroids (prednisolone) because most lymphocytes are rich in steroid receptors.
3. Synergistic drug: adjunct chemotherapy e.g. vincristine. We give a combination (up to 8 drugs) for better effect and less side effects.
4. Intra-thecal Methotrexate: we give it on a weekly basis to prevent and treat brain metastasis. If there was already brain metastasis the treatment of choice is brain radiotherapy in high doses; to decrease the radiotherapy dose we give methotrexate along with it.

* Prognostic factors:

1. The most important is age:

* Less than one year to 18 months has the worst prognosis because:
* They have the highest count.
* Bi-lineage expressing both AML and ALL. These have the biggest liver and spleen.
* The highest number of mutations e.g. t(4,11).
* Chemotherapy can’t eradicate it.
* Above 9 years: because they mostly come with T-cell that has a brain predilection. You must prepare the child for transplant. Patients between 2-9 years have pre-B cell leukemia that carries the best prognosis.

1. WBC count: the higher the number the worse the prognosis. It’s an independent prognostic factor. Less than 10 have the best prognosis, 10-50 is moderate, and more than 50 has the worst prognosis.
2. Mediastinal mass: indicates T-cell leukemia, which is bad.
3. Massive Generalized lymphadenopathy and organomegaly (reaching below the umbilicus). Organomegaly above the umbilicus is of no prognostic factor.
4. Philadelphia positive: they resist chemotherapy.
5. Hypoploidy: e.g. monosomies carry a worse prognosis than polysomies.
6. Presences of any pre-leukemic syndrome.
7. Myelodysplastic syndrome.

* Drugs toxicity: (the following drugs are for induction)

1. Vincristine:

* Peripheral neuropathy affecting:
* Mainly the lower limb (can’t get up and absence of the deep tendon reflexes.
* Paralytic ileus: complaining of severe abdominal pain, distension, vomiting and constipation because the bowel is paralyzed then you must evacuate the stool if the constipation lasts for 15 days.
* Ear pain due to neuropathy and not infection therefore its not treated by antibiotics.
* Wrist and foot drop which are irreversible and are the only indication to stop the drug and is a contraindication to use it again.
* SIADH: the patient comes with edema.
* All these complications don’t cause bone marrow suppression only neuro-suppression.

1. Adriamycin:

* Hemorrhagic cardiomyopathy (most serious); therefore, you have to monitor the cardiac function by echocardiography because it might lead to irreversible heart failure.
* Alopecia.
* Bone marrow suppression.

1. Asparaginase: it prevents amino acid synthesis (no cells and hence no blasts) and is given I.M.

* Anaphylaxis: can appear after the 9th or 10th dose with no warning, that’s why it’s only given in the emergency to watch for severe reaction.
* Abdominal pain: due to necrotic pancreatitis, we order amylase (every other day). The abdominal pain in vincristine is due ileus, while in asparaginase its due to pancreatitis.
* Hypofibrinogenemia: if bleeds, stop the medication and treat with fibrinogen and if it is not available, use fresh frozen plasma.
* The patient is in remission when:

1. Signs and symptoms disappear.
2. No organomegaly.
3. Normal CBC.

* When the patient is in remission put him on maintenance therapy (6-mercaptopurine is the drug of choice) we can also give methotrexate.
* Bone marrow transplant remains the treatment of choice in leukemia.