SHEET NO. 21

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

DONE BY : Sally Abdulnour & Farah H Albadrani

SCIENTIFIC CORRECTION : Sally Abdulnour & Farah H Albadrani

GRAMMATICAL CORRECTION :

DOCTOR : Dr.Malik

السلام عليكم

كلام الدكتور باللون الأسود وكلام السلايدات باللون الخضر.

Cancer Incidence and Mortality

• Cancer is a common disease. One in three people in the Western World contract cancer and one in four die from it.

• The cure rate is 50%

• Cancer is strongly age-related, the incidence rising rapidly at age 50.

• Cancer is a collection of about 200 different diseases. Abound 10% are leukemias (blood cancer) and lymphomas (lymph nodes cancer) and the remaining 90% are solid tumours, mostly epithelial carcinomas.

- The problem is that almost every patient has a different type of cancer, even if two patients have the same stage of cancer, the main problem of cancer is heterogenicity (a heterogeneous population of cells growing within the body of the patient). So every patient will come with different cancer even though they both have the same level/stage.

❖ Abolishing cigarette smoking would lower cancer mortality by about 40% in America/Europe. Lung cancer is 100% fatal. 95% of sufferers are smokers. 1 in 7 smokers succumb. In 1900 lung cancer was virtually unknown. It was the American cigarette, invented in the late 1800's, and WW1 that transformed the Western World's cancer patterns. There is currently a smoking epidemic in Asia and Africa and lung cancer is sure to follow. Bladder and cervical cancer are also linked to smoking.

Tumour Biology

•Cancer is a genetic disease that results from the accumulation of mutations that:

1. Activate dominant oncogenes("oncogenes= ongoing genes " are the genes in our body that are responsible for the growth of the cells, cells growth are driven by many genes) in the growth proliferative pathways send false positive signals that constitutively drive the proliferative cycle.
   - If we didn't control the oncogenes, and a mutation occurred, they will produce too much positive signals toward proliferation.
2. Inactivate tumour suppressor genes ("tumour suppressor gene = cell cycle suppression gene" the opposite of oncogenes means they are the negative guys, they control the cell cycle by stopping it from getting out of the normal conditions) which function in various biochemical processes.

In cancer there are two main steps:

1. start with a mutation in oncogenes.
2. developing the mutation toward tumour suppressor genes mutation, so we lose the control on the cell.

•To much massages from oncogenes" on going," with less activity of the cell cycle suppression genes.

3. Damage is also done to DNA repair genes so that, over time, giving rise to hypermutability and tumor heterogeneity.

- Mutation occurs in the DNA repair genes (check points), We should check the Cell at the replication phase in case any mutation happened, the tumour suppressor gene will correct the mutation.
- In normal condition 3 different nucleotides between the mother cell and the 2 daughter cells occurs in every 3.3 billion nucleotides within the cell.
- In the case of cancer when mutation occurs in that DNA repair gene, every cell division can reach about 1000 mutation, means that the daughter cells are different than the mother cell and same implies to granddaughter cells, ending with a big problem.
- The ending result is formation of lump and cancer that has different components, it starts in a certain way and then gradually start to change (differentiate) more and more every time the division increase (each time the lump/cancer gets bigger) which will cause more and more differentiation.

❖ The outcome is that tumour cells relentlessly drive through the proliferative cell cycle and generally lose the capacity to differentiate.

❖ harder to differentiate between cells and become close to the idea of "non differentiated cell"

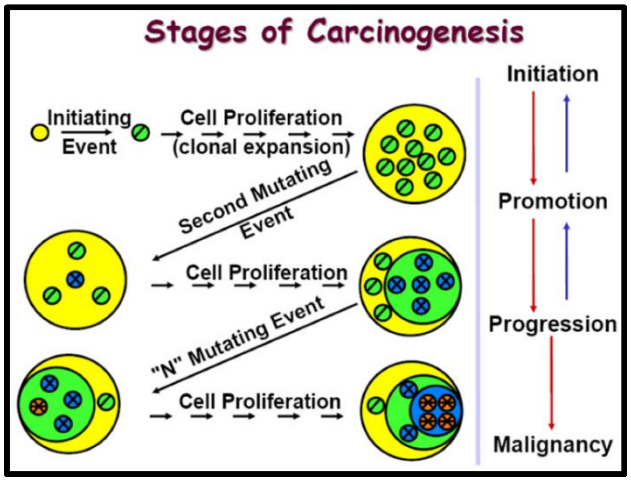
Until this point we didn't reach the malignancy, still only a tumor.

4.to become malignant

A. The mutated cells have to acquire the capacity to avoid immune detection to metastasise.

B. To be able to induce angiogenesis in order to provide themselves with a blood supply.

- Once the lump reaches 1g it starts to send signals to blood to supply them" like it's a whole organ by itself " like oxygen and nutrients, signals are send by vascular endothelial growth factor & fibroblast growth factor , they work by developing the vessels toward the cancer, this mechanism is called angiogenesis.
- Why T cell doesn't attack the cancer cells? Because all the mutations that generate in every division produces a cell that is capable of avoiding the immune cells, so immune system is seeing and knowing the cancer cell but with no response because the immune system have been trained not to recognize the cancer cells and consider it as a friend.



1.monoclonal cancer cell which at the initiating event changed the yellow to green followed by proliferation (oncogenes).

2. Then the green thar is inside the yellow started to mutate (acquire a mutation) and turned into blue (tumor suppresser gene).

3. changing into red (mutation in DNA repair gene).

- When we have reached a level by which 3 colours are obtained, this means it started to grow by uncontrolled proliferation, then a malignancy takes place, how? By becoming able to escape from the immune system & sending to endothelial cells for blood supply (the need to be supplied by the angiogenesis process).
- These are all considered as solid tumours.
- Liquid tumours are the same as solid but the main difference is at the last stage (angiogenesis doesn't occur, because they are already in the nutriment location and don't go lump, only stay as a single cells separated from each other).

About the following picture:-

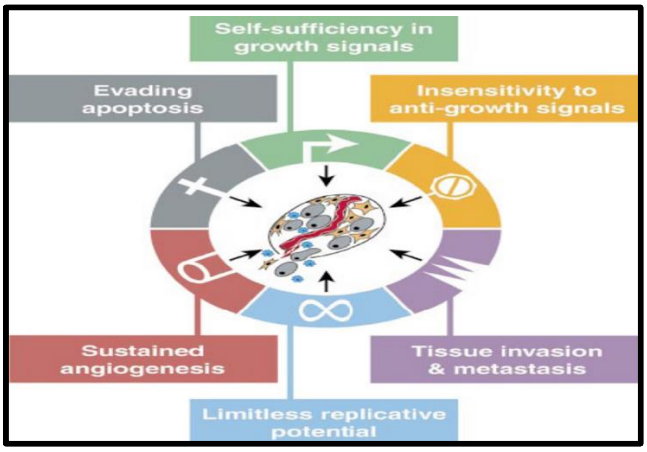
Cancer cell have 6 main qualifications:

1. self-sufficiency in growth signals. 2. insensitivity to anti-growth signals.

3. tissue invasion & metastasis; after the cancer cell gotten all the supply it needed and oxygen, it starts searching for other places, because angiogenesis is not enough by itself (not sufficient) so some cells that aren't receiving blood supply and oxygen, in this case the cells undergo changes like epithelial cells become Mesenchymal cells, we call this mechanism " epithelial to mesenchymal transmission " a needle-like shape and move to other places, such as lung cancer which is epithelial cells but under hypoxia it's transmitted into needle-like cells, by this transmission now it can escape to other places that can supply them (when cancer metastasize, our patient will be 99% dead).

4. limitless replicative potential.
5. sustained angiogenesis
6. evading apoptosis; cancer cell is a cell that divides but don't undergo apoptosis (cell that cannot die) and avoid this process mostly by enzyme telomerase by producing new telomeres in cells , so telomeres are not gradually degreasing, and there are other mechanisms by which cancer cells causes apoptosis.

Normal cells die because when telomerase is decreased in chromosomal ends then the cell is going towards programmed cell death (apoptosis).



- Yearly 18.7 million worldwide people are diagnosed with cancer.
- 7.8 million deaths from cancer every year.

Jordan doesn't have high rates of cancer not like western Europe areas which have very higher rates of cancer, the genetic origin "Anglo-Saxons", every 1 in 3 men will have a cancer, and 1 of 4 ladies in the west will have a cancer.

- In Jordan 1 in 9 men will have a cancer.
- Lifestyle play a big role in cancer like alcohol, smoking, genetic material and stress.

Cancer treatment

- There are three major approaches to the treatment of the common solid tumours:

1. SURGERY (patient that goes with only surgery is a lucky patient) Consider as a rate limiting factor.

2. RADIOTHERAPY (mostly death) some times we can't go surgery without taking radiotherapy before or even if we can't do surgery. Consider as a wild way.

3.CHEMOTHERAPY (mostly death)

- If it was a pancreatic cancer , pancreas are mostly diagnosed late, the patient will die within 6 months if we treated him, if we didn't within 2 months or 3 he will be dead, similar with brain cancer, stomach cancer, if no surgery in liver cancer then within 1 year patient is dead.

- If the treatment was in its beginning and surgery is done by taking all the lump without forgetting any piece of it, for example kidney cancer if it was diagnosed at stage 1 or 2 and remove the whole kidney with all lymph nodes, your patient have 50% chance to survive and being alive for more than 5 years, even 10 years.

❖ The primary tumour is removed by surgery. If it hasn't metastasised yet, then the surgery may prove curative.

• Radiotherapy, irradiation with high energy X-rays (4 to 25 MeV), may be applied subsequent to surgery to help prevent regrowth of the primary tumour. (to make sure no cells or edges are not treated).

• Surgery plus radiotherapy is a common treatment modality.

• X-rays kill tumour cells (and healthy normal cells in division) by free radical damage to DNA that results in double strand breaks which are lethal to cells at mitosis.

- We break the DNA strand within chromosome, then the cell tries to make division, but it dies.

• Tumours that are not resectable may be treated by radiotherapy alone, in which case treatment is largely palliative.

- Then once that surgery doesn't work, we start with radiotherapy.

Palliative: treatment with only trying to make control of the growth of the cancer cells, but we don't cure the patient, example like Nasopharyngeal carcinoma that are close to trachea and vocal cords and it can't be removed so we use palliative treatment, within 2 years patient will die.

- About 18.7 million patients with 7.8 million meaning that 50% almost to survive or die.

• Most of the 50% cure is affected by surgery and radiotherapy on non-metastatic tumours.

• If the disease is found to be metastatic then systemic chemotherapy is administered after surgery and radiotherapy. (we are talking about palliative therapy more than treatment)

Cancer Chemotherapy

• Cancer drugs are not specific for cancer cells but are cytotoxic to all proliferating cells in cycle.

• Their major unwanted toxicity is damage to bone marrow function and to the epithelial lining of the gut.

• Generally speaking, these are the dose-limiting (rate limiting) toxicities for those drugs.

The Goal of Cancer Treatments

• Curative

– Total irradication of cancer cells – Curable cancers include testicular tumors, Wills tumor.

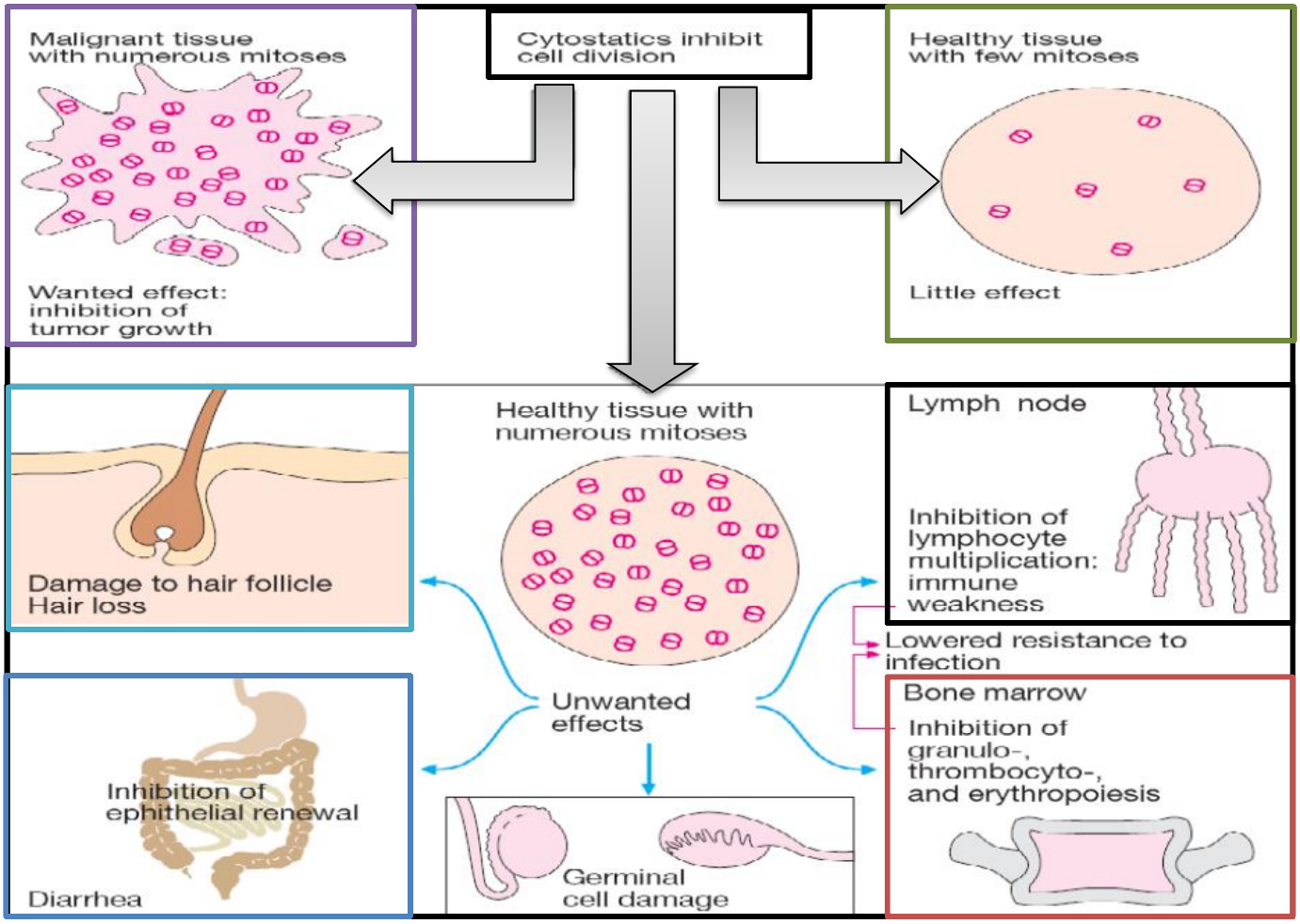
• Palliative

– Alleviation of symptoms – Avoidance of life-threatening toxicity

– Increased survival and improved quality of life

• Adjuvant therapy

– Attempt to eradicate microscopic cancer after surgery, e.g.breast cancer & colorectal cancer.



About the previous picture which we have to memorize VERY WELL…

- cancer drugs (chemotherapy) are given to patients through IV, then it enters the body and goes to malignant tissue with numerous mitosis and this leads to wanted effect which is inhibition of tumor

growth but there are unwanted side effects in healthy tissue with numerous mitosis such as the hair follicle (alopecia) because the hair follicles will undergo divisions and cancer treatments are not selective (they inhibit cancer cells proliferation and also inhibit the hair follicles and this causes hair loss -alopecia-).

- lining of the epithelial gut: in GI, cells are renewing continuously but by giving cancer drugs we are inhibiting epithelial renewal (which is daily basis); this causes diarrhea, nausea and vomiting.

- lymph nodes: inhibition in lymphocytes multiplication occurs, in addition to immune weakness (cancer patient taking chemotherapeutic drugs is an immunocompromised patient).

- bone marrow suppression: anemia due to lost RBCs, ischemia, hypoxia, thrombosis due to lost platelets and all these problems are caused by cancer agents.

- healthy tissue with few mitosis: we are talking about the heart, kidney, liver, brain and all organs that don't have mitosis and hence won't be affected (even if there was a certain effect but in general they are not affected since they don't reproduce).

To summarize:-

Cancer drugs in general (all chemotherapeutic drugs) they produce bone marrow suppression (they could be disparate in effect), lymph node suppression, alopecia, hair follicle loss and renewal of epithelial gut is decreased as well; in addition to germinal cell damage (when the patient become sterile -no spermiogenesis-) since sperms are reproducing fast in men but chemotherapy will decrease them and this is what causes sterilization (inhibition of spermatogenesis) but after 2-3 months; spermatogenesis will be back to normal. In ladies, the oocytes are present and that what makes us afraid of the mutations that occur and that is why we advice to avoid pregnancy within the first 5 years (4-5 years from last dose of chemotherapy and presence of pregnancy).

Q/ Although we gave treatment to the patient and applied surgery, his life expectancy is still -for ex- two to three years or even one year, so what happened to cause this?

A/ even if we are seeing the cancer, sometimes it is metastasized without the ability to see it and this is one of the reasons for treatment failure.

Chemotherapy is able to cure only about 10-15 % of all cancer patients

Reasons for treatment failure

Either the patient:-

(1) presents with a tumour that is already non-responsive (when we give the treatment but the patient is not responding to it).

(2) the tumour initially regresses only to return later in a drug-refractory form and this is the most common case since most cancer cases in Jordan like breast and colon cancers the patient are responsive but only to return later in drug-refractory form (when we treat the patient and he is responsive and goes back to normal BUT within 1-2 years there will be recarance in the refractory form -drugs become not effective).

> The main problem in treatment failure is DRUG RESISTANCE not a lack of selectivity for tumour cells.

The origins of resistance lie in the following issues:-

(1) Genomic instability and hypermutability

- The de-regulated genome →→ genetically heterogeneous tumour
- Damage to DNA repair genes is critical →→ → more heterogeneousity as the disease progresses.

• From a pharmacological perspective at the biochemical level the tumour is a constantly changing target (cancerous cells and therapeutic cells are changing-for ex: changing cancerous cells from epithelial to mesenchymal or from mesenchymal to epithelial, same goes for drug-resistant and non drug resistant cells through mutations and hyper-mutability)

- but the primary tumour can be biochemically distinct from metastatic deposits that ran away.

- one person's colon cancer can be biochemically different from another person. (and this is what we talked about when we said -don't consider a bill for every patient- since we have high variation for each patient -genetic, weight, age, sex, gender and liver's diseases variations-).

- as for hypermutability, so the colon cancer that will be diagnosed for patient A is different from the one diagnosed for patient B and this is the main problem that we are facing since the treatment we are using is the same (same bill) for all these patients even though they have different cancers.

(2) Tumour Cells Are Not Immunogenic

- Tumour cells evade immune detection by down-regulating their MHC antigens (inhibiting histocompatable antigens).

- the new science is telling us that cancer cells are training cells of the immune system on how to deal will them. How did we know? When we remove the lump from the patient we will see that there are cancerous cells and there are lymph nodes living next to them but there is a message coming out from cancer cells to lymph nodes telling them that they are friends ☺ and we call them (check point inhibitors) which means that they are inhibiting the things that T-cells do to cancer cells so they inhibit it by teaching T-cells that they are their friends ☺.

- So they can't be recognised by antigen-presenting and activated killer T-cells.

(3) The Numbers Game

• 1 x 10^8 tumour cells are visible on an X-ray.

• 1 x 10^9 cells is a palpable lump weighing a gram.

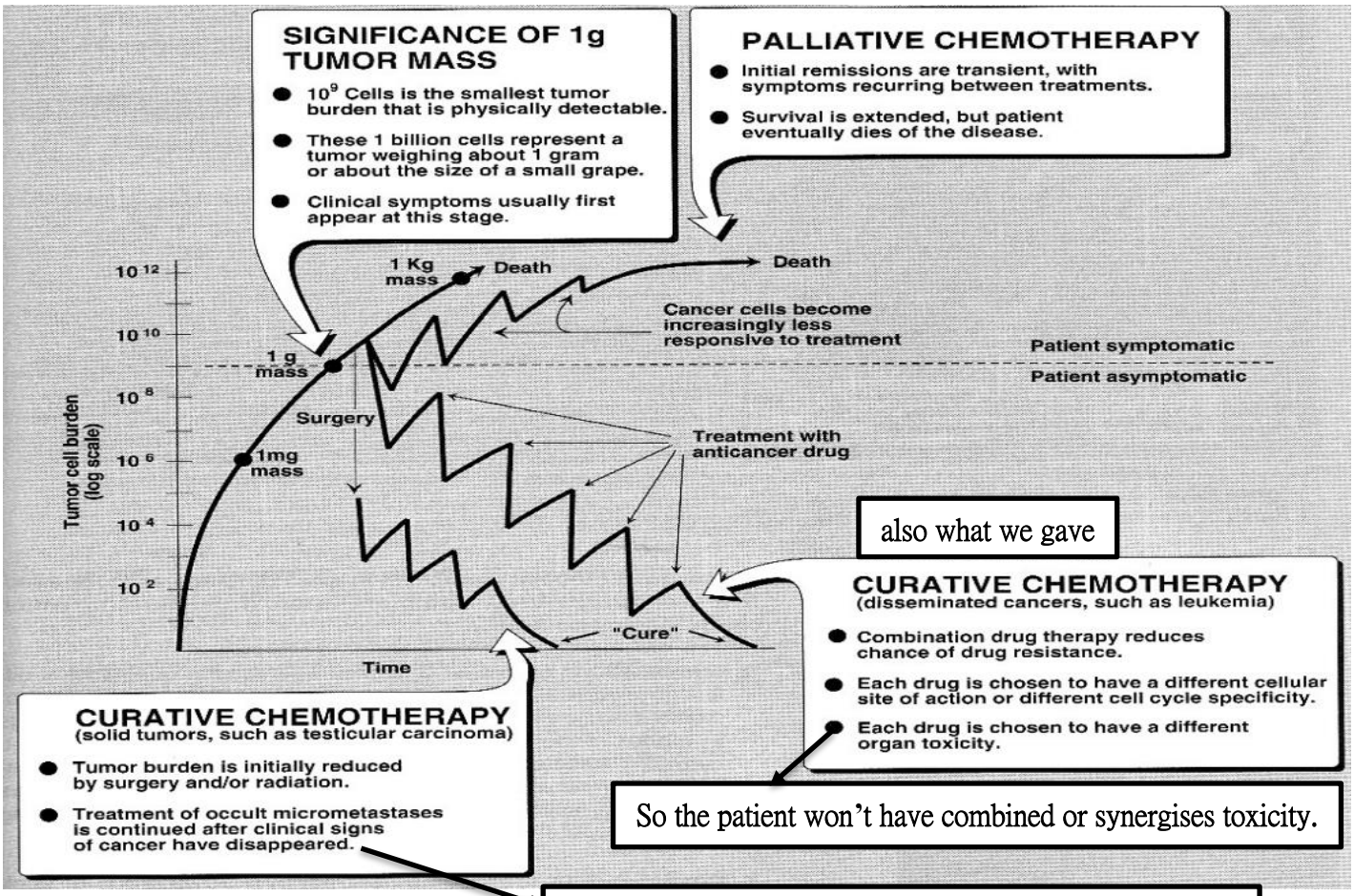
• 1 x 10^{12} cells weigh a kilogram and the patient is dead.

• Cancer is hard to detect in its early stages and may already have grown to 10^{10}- 10^{11} cells at presentation.

- most importantly you've got to kill every single cell by drug treatment. (in chemotherapy we will kill every replicating cell, yes we applied surgery to what we are able to see -bigger than 10^8 or 10^6 (according to a new science in Germany)- so we remove 10^6 and for what is beneath it we can't do nothing so we give cancer drugs to eliminate these cells).

- No immunological moping-up of residual tumour! (as we took with dr.Manar, the bacteria is living in our body but when we give an antibiotic we lower it beneath the infective load and same goes to viruses, so as long the immune system is able to keep it beneath the infective load there will be no infection BUT this is not the case for cancer, cancer has teached the immune system that it is a friend; so we have to kill every single cell of cancer).

- If there are 10^{11} tumour cells present (100g), killing 99.99% of them leaves 1 x 10^7 residual cells.
- one L1210 leukaemia cell will kill a mouse.



(all chemotherapy-treatments- mentioned above have been mentioned by the doctor in the lecture so they are considered required and we should memorize them) ☹

In the previous picture:-

- the cancer is growing from 0-1mg mass and it didn't take very long to reach 1 gram nor did it take too long to reach 1 kg and eventually leading to death.

Q/ how can we intervene?

A/ if we could do surgery, cancer will decrease from 1 gram (10^9) to 10^4 so then we give CURATIVE CHEMOTHERAPY (we remove the testis in case of testicular cancer and then: tumor burden in initially reduced by surgery and/or radiation, and treatment of occult micrometastases (which we can't see) is continued after clinical signs of cancer have disappeared with the treatment.

- about the importance of number game --> if there is no surgery then there will be death.

(4) Poor Tumour Vasculature

• Tumour masses can only grow to a diameter of about 200 microns before they run into trouble with nutrient supplies.

- To grow larger they must develop their own vasculature which they do by producing angiogenic growth factors which are the vasculo-endothelial growth factor, fibroblast growth factor and also the platelet derived growth factor.

- However, these blood vessels are of a poorer quality than normal which leaves parts of the tumour without nutrients and oxygen. (the tumor is sending and bringing blood supply but it is not reaching everywhere so poor tumor vasculature occurs).

- tumor generates regions of hypoxia in the tumour mass where cells come out of the growth cycle and sit, alive but nonproliferating, in G_0. (cells leave the cycle and enter G_0 but all cancer drugs (99%) work on cycling cells -cells inside the cycle- so if the cell is not in the cycle it won't die)

- Unfortunately, hypoxic cells in G_0 are resistant to all anticancer drugs.
- Thus, hypoxic cells become a pharmacological sanctuary from which the tumour can be repopulated after a round of drug treatment when surviving cells may get the opportunity to be re-oxygenated. (if we kept giving chemotherapy but with no use since cells have got out of the cycle because there is no blood supply reaching it, so cells solution was to adapt inside hypoxia…so these cells resist all the drugs and after 2 years it will come back to live and cause cancer and we said that cancer is a monoclonal origin; if we left one single cell of this type then this single cell will bring cancer again.

(5) Deregulation of apoptosis

THIS IS THE BIG DADDY OF THEM ALL! (0_0)

-The genomic instability of tumour cells inevitably leads to deregulation of the apoptotic pathways.

-This results (we are giving drugs but the cell won't undergo apoptosis) in a generalised reduction in the sensitivity to all forms of cellular insult. THE REAL BRICK WALL.

So there are 5 problems with the cancer cell:

1) we are treating 109 cells and each cell is different.
2) the immune system is not working.
3) the detection system (X-ray) can't see beneath 106.
4) hypoxia cells aren't detectable so they undergo repopulation.
5) a lot of cells metastasized and cancer would reoccur.

THE END ❤