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Chemotherapy as a Cancer Treatment

Treatment of cancer is very harsh, and it is associated with several side effects; because cancer drugs are not selective and target all actively dividing cells. There are typical side effects that are associated with such cancer; which include: alopecia; bone marrow suppression; immunosuppression; gastrointestinal tract disturbances (diarrhea, nausea, vomiting…).

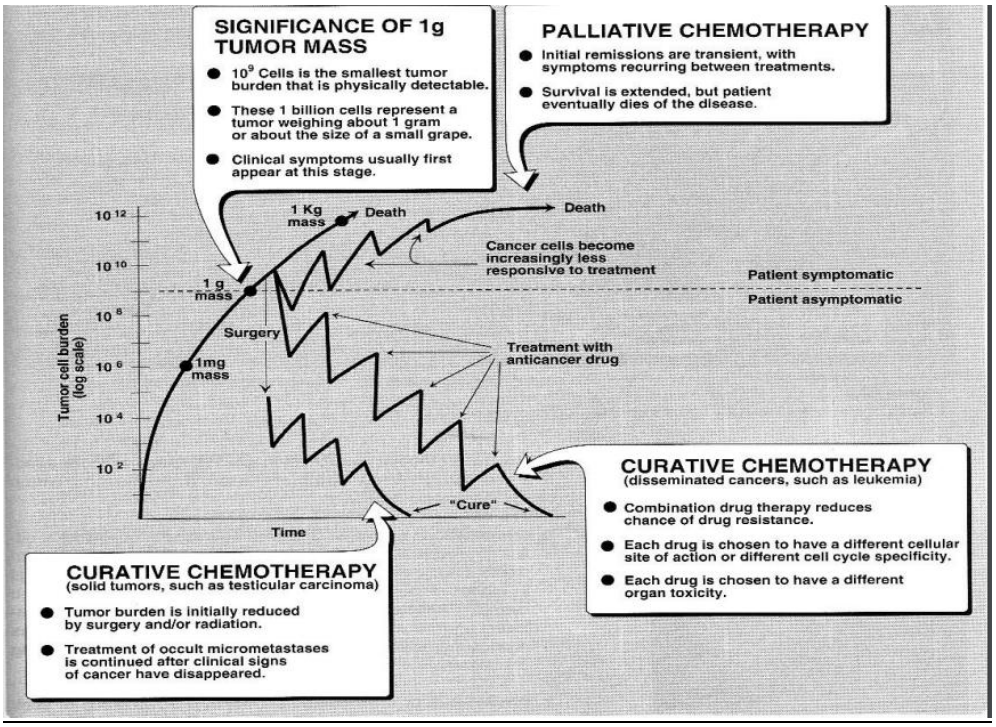
Breast Cancer Chemotherapy

Introduction to breast cancer

Brest cancer, colo-rectal (colon) cancer and lung cancer are the most common cancers in Jordan (983). 5 to 7 women per 100 women (6-7%) will have breast cancer in Jordan, and the numbers are higher in western countries, and numbers are increasing. Lifestyle habits have a very influential effect on these numbers.

For example, above-30-years-of-age pregnancies are becoming more common, in addition to the use of oral contraceptives, and breastfeeding of newborns is getting less common, in addition to the fact that more and more women work outside home, and more and more women develop depression and stress, all these facts prevent the normal biological life of the body, which increases the incidence of developing breast cancer(adverse effects on both the mother and the child) . Men can also get breast cancer, especially those with BRCA 1 or 2 mutations.

Importance of surgery in treating cancer



We usually detect cancer when the tumor cell burden Is about 109 . chemotherapy alone is not typically a sufficient therapy for the effective reduction of the tumor cell number. Surgery increases the chance of the cure of the cancer; because it contributes to the removal of the solid tumor, which decreases the cancerous cells' number dramatically.

However, after surgery, not all cancer cells are removed; because malignancy involves cells that are able to escape and metastasize. Such cells are targeted by chemotherapy after the surgery.

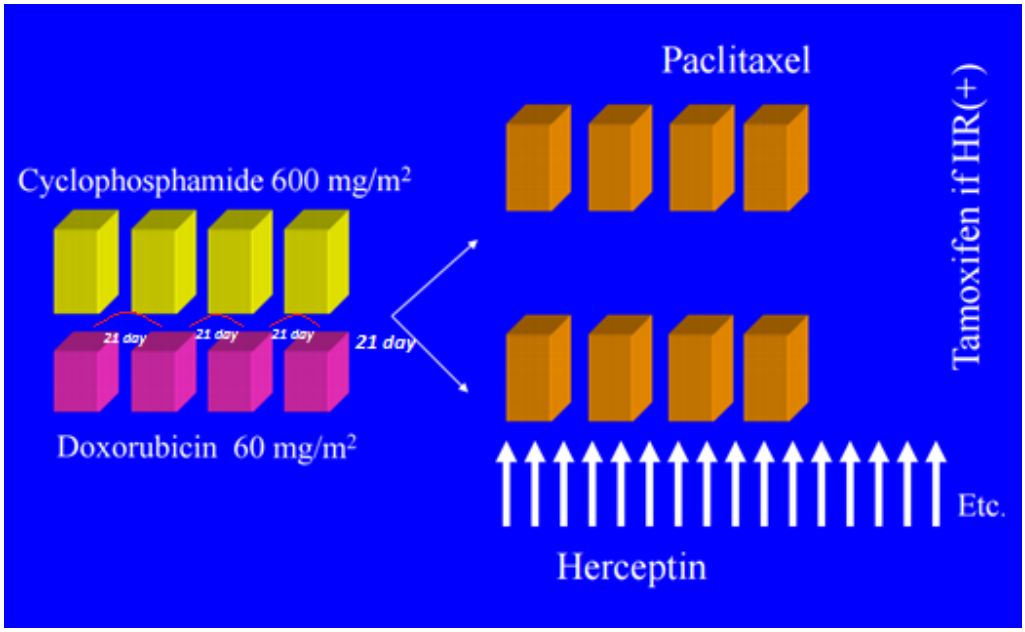
all in all both surgery and chemotherapy are required for the effective treatment of malignancies.

Why is it that crucial to target the malignant cells that escape removal through surgery?

It is because cancer is of monoclonal origin and the survival of a single malignant cell will eventually result (of undetected and treated) in tumor formation.

Breast Cancer Drugs

The usual chemotherapy of breast cancer involves the drugs that are shown in the diagram bellow.



A. ***Chemotherapy***

1. **Doxorubicin**:

Anthracyclines Are the most commonly used anticancer drug. Doxorubicin is the most common one, having activity against a wide range of solid tumors. Doxorubicin prevents topoisomerase II from rejoining DNA, which renders the DNA fragmented (DNA strand scission.) -This drug is similar to quinolones, but targets dividing human cells rather than bacteria- It has High affinity binding to DNA through intercalation, resulting in blockade of DNA and RNA synthesis. Doxorubicin also binds to membranes which alters fluidity.

Side effects:

- The four typical side effects of cancer drugs (alopecia; bone marrow suppression; immunosuppression; gastrointestinal tract disturbances (diarrhea, nausea, vomiting…)
- Cardiotoxicity: This cardiotoxicity may be a result of the generation of free radicals and lipid peroxidases. This kills myocytes, which leads to congestive heart failure CHF (irreversible heart failure). This side effect is *dose-dependent*.

Dosing:

4 cycles of Doxorubicin are given to the cancer patient, But why 4 cycles?

The probability of developing impaired myocardial function based on a combined index of signs, symptoms, and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300mg/m2 of Doxorubicin, 3 to 5% at a dose of 400 mg/m2, 5 to 8% at 450mg/m2، and 6 to 20% at 500 mg/m2 (in cancer treatment, doses are given per m2, because cancer drugs are very toxic, and this way is muchmore accurate than calculating doses according to the body mass index BMI.) The risk of developing CHF increases rapidly with increasing total cumulative doses of Doxorubicin in excess of 400 mg/m2. So, the theoretical limit for Doxorubicin dose is 400mg\m2, but practically, the safer limit equals to 350mg\m2. By looking at the previous diagram, you can see that Doxorubicin is given as 60mg/m2 × 4 cycles which equals 240mg/m2. In more aggressive cases, the dose is raised to 80mg\m2 × 4 cycles, with a cumulative level of 320mg\m2. (That's why Gentamicin (amino glycoside) is only used for one week; because the chance of developing nephrotoxicity increases drastically after this period due to the accumulation of the drug beyond the safe cumulative level)

2. **Cyclophosphamide:**

Alkylating agents bind irreversibly to DNA and function by crosslinking the two Watson-Crick strands, thereby inhibiting strand separation and preventing DNA replication. These results with DNA fragmentation (strand breaking); the same output of Doxorubicin (cidal effect.) Cyclophosphamide is the most commonly used alkylating agent used in lymphomas, leukemias, sarcomas, carcinomas of breast or ovary, as well as childhood malignancies.

Cyclophosphamide can be given orally and/or intravenously IV. In cancer treatment, cyclophosphamide doses are given IV in 4 cycles. But in metastasized breast cancer treatment, a maintenance therapy should be applied, and that is achieved by the oral administration of Cyclophosphamide, especially that IV maintenance therapy is not practical for long durations.

Side effects:

- The four typical side effects of cancer drugs (alopecia; bone marrow suppression; immunosuppression; gastrointestinal tract disturbances (diarrhea, nausea, vomiting…).)

- Cystitis (inflammation of the urinary bladder) may result from Acrolein, which is Cyclophosphamide metabolite, results with urinary bladder inflammation. To prevent that, Cyclophosphamide is co-administered with N-acetylcystein or 2- mercaptoethanesulfonate (mesna). Both are thiols that neutralize acrolein (chemical antagonism.)

So far, we used 2 drugs that have 4 common side effects at the same time, isn't that contraindicated?

- We do not have a choice, especially that these shared side effects are common for all chemotherapeutic drugs. Moreover, studies show that the maximum effect is unfortunately achieved when using a combination therapy of these 2 drugs (synergistic effect.)

- The good news is that doxorubicin and cyclophosphamide do not both cause cardiotoxicity and cystitis.

- It also should be noted that the administration of the third anticancer drug "Paclitaxel" is postponed in order to minimize the resulting synergistic effect.

Note: each cycle of Doxorubicin and Cyclophosphamide lasts for 3 days, and a 21-day rest interrupts the cycles, to allow bone marrow growth.

3. **Paclitaxel:**

After 21 days of the 4th cycle of Doxorubicin and Cyclophosphamide, we start a therapy of Paclitaxel cycles (4 to 8 cycles). It is one of the mitotic spindle inhibitors. In M phase, mitotic spindles pull chromosomes towards centromeres. The TAXANES, of which Taxol is the best known example, are isolated from the yew tree. This drug binds to the mitotic spindles preventing the de-polymerization of the spindles. (the pulling of the mitotic spindles)

Other drugs prevent the attachment of the spindles to the chromosomes during M phase of the mitotic cycle and they are known as the polymerization inhibitors).

Mitotic spindle inhibitors

Type	***Name of drug***	***Use of drug***	***Source of drug***
Inhibition of formation (polymerization inhibitors)	Vinca alkaloids (explained in the 3rd year)	To treat hematologic malignancy	*vinca rosea*
inhibition of degradation (de-polymerization inhibitors)	Paclitaxel	To treat breast cancer	western yew tree

Side effects:

- The four typical side effects of cancer drugs (alopecia; bone marrow suppression; immunosuppression; gastrointestinal tract disturbances (diarrhea, nausea, vomiting…)
- The taxanes are generally more toxic than the Vinca alkaloids and side-effects include myelosuppression and Peripheral neuropathy; which is manifested by neuromuscular plate's pain, and severe joints pain. This side effect depends on the dose, but more importantly on the patient body. So, there is no dose limit that determines the level of the drug after which there is a higher risk of developing Peripheral neuropathy, what is actually done in this case is that patient is given a specific dose and he/she is monitored for any side effects and if the patient develops Peripheral neuropathy then the dose is reduced.
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In these drugs, we've discussed many side effects, but we still use such therapies; since benefits outweigh the risk.

Biologically-targeted therapy

4. **Herceptin (Trastuzumab)**

Note: -mab suffix stands for (monoclonal antibody); which binds to a receptor, preventing its activity.

About 20-30% of breast cancers overexpress HER-2 protein (usually because of gene amplification), so it is a driver of the cancer. Monotherapy with anti-HER-2 monoclonal antibody (trastuzumab or Herceptin) has a 30% response rate in HER-2 positive metastatic breast cancer.

This therapy is targeted to HER-2 positive breast cancer cases (pharmacogenetics; treatment depends on the patient's genetic make-up and proteins levels – personalied medicine), and other cases cannot be treated with it. A biopsy is examined to know if the cancer is HER-2 positive, this determined using the FISH test (which is similar to western blotting and immunohistochemistry techniques), and the principal concept of such test is the binding of an antibody to its the target (HER-2 protein in this case) usually, HER-2 positive breast cancer is more aggressive than HER-2 negative.

Combination of trastuzumab Reduces recurrence by 1/2 & deaths by 1/3 when added to chemotherapy in early stage breast cancer. of course all of this occurs after the performance of surgery.

Dosing:

Trastuzumab is administered as injections; one injection every 28 days (usually 12 injections are given as a total)

Side effects:

- Trastuzumab plus anthracycline (doxyrobicin) results in a 20% incidence of cardiotoxicity. So, the combination of these two drugs is avoided, and Trastuzumab is given with Paclitaxel, instead.

- The 4 typical side effects of chemotherapy do not occur with Trastuzumab; since it is a targeted therapy for HER-2 positive patients.

- What about normal cells that have HER-2 protein? Usually normal cells have low amounts of HER-2 protein, and they do not depend on it primarily like cancer cells do. So, this therapy does not affect normal cells.

The FISH test does not only examine HER-2 proteins over expression but also if the patient is ER and PR positive (estrogens)

B. Hormone antagonists

Tumors derived from hormone-sensitive tissues may be hormone-dependent. Their growth can be inhibited by hormones with opposing actions, hormone antagonists or inhibiting hormone synthesis.

- ***Tamoxifen***

Selective estrogen receptor modulator (SERM), have both estrogenic and antiestrogenic effects depending on the type of tissue; it is found to be estrogen antagonist in cancer cells (breast tissue,) but agonist on bones and endometrium.

Usage:

- Recurrence of breast cancer accounts for 30-40% of cases; which indicates that some cancerous cells still exist even after chemotherapy. To prevent recurrence, recurrence-prophylactic therapy with Tamoxifen is applied.

- Tamoxifen is also used prophylactically in women who are at high risk for developing the disease (BRCA 1 or 2 mutation; family history); since it has been shown to decrease the incidence of breast cancer.

- It is taken daily orally for 5 years.

Side effects:

- Mainly, menopause-like symptoms, which include hot flashes, depression and blood clots, (rare.)
- Increased risk of uterine cancer; because it works as an agonist of estrogen in the endometrium. This sets a limit for the doses of Tamoxifen; which is used for 5 years only (daily and orally.) After 5 years the incidence of developing uterine cancer will increase from (1-1.5%) to (2-2.8%).

As we discussed before; even if the consequences and the sides effects are harsh, we've got no choice but to apply chemotherapy in breast cancer treatment.

A doctor can bury his mistakes but an architect can only advise his clients to plant vines.