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Editorial

Cancer Disease Models

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Independently from tumor stages and treatment modalities, Cancer cures are nowadays common in Medical Oncology.

A plethora of different advanced tumor types can be tackled with chemotherapy and with the new design emerging medicines.

Anecdotal is George Bernard Shaw play (1909) "The Doctor´s Dilemma" which makes this author someone related to a seer. An actor says: "there is at bottom only one genuine scientific treatment for all diseases, and that is to stimulate the phagocytes". Really, Immuno-oncology was born at that moment!

Cancer has several common biological features, such as the self-sufficiency in growth signals and its insensitivity to these signals, limitless replicative potential, sustained angiogenesis, apoptosis and immunologic evasion, and finally its paradigm, metastases.

From a clinical and pathophysiological point of view, we can imagine Cancer as models of diseases.

The first one (Model 1), comports advanced chemo-curable tumors, for e.g. germ cell Cancers, some pediatric and adolescent tumors such as lymphomas, leukemias, bone sarcomas, and I add nasopharyngeal cancer.

These diseases are highly chemo-sensitive, highly radiosensitive, and second and third lines of chemo rescue are a reality for many of them. The reason for chemo-sensitivity is probably due to the existence of a peculiar tumor genomic profile, for e.g. with less DNA initial content from the cell of origin (haploidy in germ cell tumors), different telomerase activity and a particular embryology: such as same site of origin for blood cells and germ cells (Wolff and Pander mesodermal islets, present since day 18 of gestation).

Nasopharyngeal Cancer is a potential curable disease, with peculiar biology (Epstein-Barr-related), geography, clinical picture at presentation, iconography (CT scans of lymph nodes with high contrast uptake), surgery is not necessary, radiotherapy is backbone and chemotherapy alone (advanced disease) or added to radio (local and regionally advanced) is a valid option.

A peculiar case of tumor can be added to this model 1: small cell lung cancer. This neoplasm comports fast cell kinetics, mitogenesis without kinases, autocrine regulation, high chemo-sensitivity (with complete responses), increase of resistance and short survival. It has a standard combination chemo, and new cytotoxic second-line agents, must "beat standards" if possible.

The second type is Model 2 and comports those tumors that at early stages can highly be cured with local maneuvers and chemo-adjuvant therapy and that in the advanced setting can be properly tackled, e.g. breast Cancer, colorectal tumors. The current knowledge here is huge, being breast, "many diseases" with constant heterogeneity, with hormone receptor modulators for hormone- responsive "slow disease", it presents new molecular subgroups just to mention HER2 +, TNBC patients and novel molecular pathways such as the novel druggable ones, AKT and PI3K.

Relapsed disease is to be treated with agents that must be active in second-third lines and non-cross resistant and if they are analogs, they must be more active and less toxic. Also, the new biology intervention is the antibody vectorized treatments such as anti-HER 2(Mabs) for breast.

Colorectal cancer can present with the wild type KRAS-associated phenotype and with the EGFR road, being treated this last, by cetuximab or panitumumab.

Prostate Cancer may fall in this group. This is a hormonal target-disease, with the androgen receptor is addicted in metastatic patients, presenting posteriorly an overexpression and aberrant function, leading to a clinical overt hormone refractory disease. New hormonal drugs and chemo were tested with success in the last 15 years for these resistant advanced patients, and in some subsets of young patients, we combine them initially, for tumor shrinkage downstaging purposes.

Model 3 comports mainly locoregionally disease types at clinical presentation.

Squamous cell head and neck cancer is the best example. A disease with different anatomical sites and with different biology, for e.g.: larynx is composed of mostly diploid cells and hypopharynx with mostly aneuploid cells. This last, makes hypopharynx more metastatic than larynx. The purpose in this cancer is the achievement of local disease control and chemoradiotherapy interventions, can preserve organs (larynx, oropharynx, oral cavity as e.g.).

Non-small cell lung cancer is another advanced locoregional tumor at presentation but is also aggressively metastatic sometimes.

Surgery followed or not by chemo is the only "curable" approach (early stages) and chemoradiation proved its worth in locoregional advanced patients.

On the last decade the molecular classification of this disease became a reality, with many complex molecular genotypes at present.

ALK positive tumors present excellent first-line targeted drugs, long maintained response periods, and at recurrence these tumors types have many novel compounds to tackle this pathway in second- and third-lines settings. The other well-known cancer route is EGFR- mutant tumors, which have also many blocker drugs, old, ongoing and in development. A great achievement is osimertinib, which targets one "operation room" in this disease, rendering patients with good clinical responses and better survival rates. The fact that some of these drugs work in the brain is a milestone, for long-term metastatic CNS control is achieved, positively impacting in survival.

Other tumors are "mid locoregional" models: esophageal cancer, gastric cancer, bladder neoplasms and cervical cancer. Even when surgery is a must for early stage disease and the only curable maneuver, chemoradiation helps in local and regional advanced disease for pre-surgery or as a definitive treatment.

In model 4, I only put ovarian cancer, an interesting peculiar disease.

It has a special natural history in the peritoneal cavity as a "local metastatic" disease. Maximal initial cytoreductive surgery is mainstay (or after neoadjuvant chemo), adjuvant chemotherapy a must, and after non-surgical-disease recurrence, second line treatments didn´t proved their worth yet. Drug resistance is always present at some time point. The best therapy for recurrent disease is surgery when possible, and we can dream with "global peritonectomy" trying to dissect all tumor implants in the peritoneum and the peritoneum itself (Sugarbaker procedure).

Model 5 comports two tumors where immunology is the main feature of their "cell physiology", being clear cell renal cancer and melanoma. Both are very angiogenic tumors, with similar patterns of metastases and are highly chemo resistant. Renal cancer has druggable pathways, and melanoma has the BRAF pathway and with an initial elusive immunogenicity, has nowadays a dissected map, where many immune medicine drugs, such as the check point inhibitors (Pembrolizumab) can treat it successfully. These last compounds render some advanced patients as curable or with better overall survival rates than in the immune-pre era.

Finally model 6, presents pancreatic cancer patients, a disease that is nearly unaffected by current therapeutic maneuvers and where still chemo clinical benefit is a major goal in advanced disease. Cure is only possible with surgery for very early disease stages (and still no screening benefit!).

Currently a lot of molecular knowledge is in development. In the past we named pancreatic cancer as a "bad disease with bad drugs", and we know now, that the main pancreatic cancer problem is its desmoplasia that nearly impedes the normal entry of drugs into the tumor. Really, an ominous pharmacokinetic issue. A schedule combining all "chemo GI drugs" is the best current approach for advanced disease (FOLFIRINOX) and even when toxic we say: "that the only toxicity is pancreatic cancer".

Some cancer models are lacking in this manuscript (soft tissue sarcomas, neuroendocrine tumors, brain cancer, liver and biliary tract, endometrial as e.g.).

Basic cancer research, clinical translation research, early and late development clinical trials and real-world treatments, are a reality in nowadays oncology.

Basic research efforts to jump from the bench side to the bedside are enormous, with many triumphs in some sides and not so in others yet. If our aim is the better understanding of cancer mechanisms for its cure and or chronicity maintenance, I see no other way that the fine dissection of neoplasia's as holistic cancer disease models.