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Review Article

Great Achievements and New Landscapes in Medical Cancer Therapy

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Chemotherapy rapidly proved its worth in different clinical cancer settings, begining with hematologic malignancies. Many pediatric and young adult tumors achieved complete remission with chemotherapy, but its use as concomitant, adjuvant and/or neoadjuvant treatment also resulted in beneficial results. The new milenium developed new techniques in molecular drug design creating novel drugs specially directed to specific cell targets, which was a solution for some traditionally chemoresistant tumors. César Milstein begun a new road with the discovery of the monoclonal antibodies, opening the landscape of the immuno-oncology that lead to present check-point-inhibitors. In the last decades, mathematical oncology and the "omics" sciences, also came to help as complementary tools for the management of this extremely complex disease in the context of a personalized medicine. Indeed, the possibility of introducing information derived from these sciences into hybrid and/or multiscalar mathematical models are nowadays the approaches most interesting and promising; with good perspectives in the diagnosis, prognosis, treatment design and follow-up of different kinds of tumors. Although at present many tumor types can be completely cured, other ones are much more difficult to eradicate, and they would be better considered as chronic diseases. In this context, some new important concepts emerge in the metronomics field, as keeping a stable tumor burden, a more benign tumor grade and a good quality of life. This mini-review addreses all these mentioned issues.

Key words: cancer, chemotherapy, drug design, immuno-oncology, "omics" sciences, mathematical oncology, metronomics, personalized medicine

Mini-review

Medical Cancer Treatment has evolved in an exponential manner since Gilman and Goodman´s mechlorethamine introduction into the bedside (10). Since then, chemotherapy rapidly proved its worth in different clinical cancer settings. Initial eye-opener results were seen in hematologic malignancies, namely complete remissions in some types of leukemias (methotrexate-Farber-related) (25) and lymphomas (De Vita-Carbone-related). Lately, adjuvant methotrexate also changed the natural disease history in osteosarcoma, becaming one of the new "overall survival drugs" in this malignancy. Many pediatric and young adult tumors achieved complete remission with chemotherapy, rendering them as curable diseases. In this way testicular cancer became the first example of a curable solid tumor (cisplatin was key factor here, Cvitkovic-Hayes-Golby-related) (11, 17). Even first conclusive clinical trial results appeared in the sixties (27), it was in the seventies that oncologists realized about the importance of chemotherapy as adjuvant in breast cancer (Bonadonna-related) (5, 7). Forty years after, two pivotal clinical trials (US and Europe) showed again the positive impact of adjuvant chemotherapy in the overall survival of this disease (6). In the nineties, three new milestones of chemotherapy were made evident. The first one was its beneficial role as neoadjuvant in laryngeal cancer as an organ preservation tool (13). Second one was its benefits in the colorectal cancer metastatic setting (irinotecan-Armand-Gandia) (2, 3, 14). The thirth one was the use of chemotherapy concomitant with radiation making use of its property as radiosensitizer. This resulted specially relevant with some tumor topographies when organ preservation is a must (*e.g.* head and neck, rectal and anal cancer).

The new milenium developed new techniques in molecular drug design creating novel drugs (named small molecules) specially directed to specific cell targets (mainly tyrosine kinases and mutated DNA segments). This approach was a solution for some

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traditionally chemoresistant tumors such us renal clear cell cancer, melanoma and lung cancer (sunitinb-Motzer-related) (26, 32). Tumor metastatic shrinkage became a reality in these malignancies. In 1975, César Milstein (Nature Letters, 1975) (19) begun a new road with the discovery of the monoclonal antibodies (which lead to the Novel Prize Award in 1984), opening in 2010 the beautiful landscape to present immuno-oncology. This let the appearance of new "monoclonal vaccines", leading to impressive clinical results in breast, melanoma, lung, kidney, lymphomas, etc. Trastuzumab in breast cancer was the first-in-class of them, being the molecular target in this case the growth factor-like membrane cell receptors (31). In other tumor scenarios cellular immunity is blocked by tumor molecules that attach to the tumor surface molecule PDL-1, evading by this way the T-lymphocyte immune surveillance (another Nobel Prize 2018, James Allison and Tasuku Honjo, were the mentors*). This novel type of treatment with monoclonal antibodies called check-point-inhibitors de-blocks the lazy lymphocytes (31). In this road of immuno-oncology there are other immune-related novel compounds and new vaccines in different phases of pre-clinical research or clinical trials.

Cancer is an extremely complex disease that involves the different levels of biological organization (16). On the last decades mathematical and computational oncology came to help with this complexity, with the final aim of working as a complementary clinical tool. The mathematical-computational modeling of complex biological diseases as cancer is nowadays addressed by the cancer systems biology (20, 4, 36). This approach has two main branches to describe the different aspects of tumor development: the continuum modeling, that uses differential equation systems, and the agent-based modeling (ABM), that defines the behavior of "agents" (cells, molecules, etc.) in response to predefined rules. Both types of models may focus at different levels of biological complexity (microscopic, mesoscopic or macroscopic). There are also multiscale models, that move simultaneously among different levels through the introduction of different spatio-temporal scales.

Multiscale ABM models allow the simulation of the behavior of different cell populations (mesoscopic level) as well as the inner physiology of individual cells (microscopic level) (37). This approach lets the analysis of phenotipic mutations, effects of oxygen and nutrient availability, adaptation to microenvironment, neoangiogenesis, and therapy respones, among other phenomena. On the other hand, relatively simple (mathematically speaking) continuum models, made at the macroscopic tissue level and based on reaction-diffusion-convection equations were able to describe not only the growth and infiltration of avascular microtumors (22, 23, 24), but also of more complex tumors as gliomas (34). In some cases, these type of models have proved to be useful for the patient-specific prognosis at the clinical level (18, 33). Many of them also incorporated the action of surgery, chemo and/or radiotherapy, turning them in good complementary follow-up and decision-making tools (30, 1). As, in general, both ABM and continuum models may be fed-up by parameter values obtained directly from the patient data, this approach lets a patient-specific modeling that adds value to the present tendence towards a personalized medicine. Nowadays, there are hybrid modeling approaches that include not only ABM and continuum techniques but also optimization, fluid dynamics, game theory and machine learning ones (9).

With the development of the bioinformatics, data mining and machine learning, the possibility of managing and extracting valuable information from a great quantity of biological/medical data derived from new molecular and imaging technologies became feasible (8). This lead to the appearance of the "omics" sciences, as genomics, proteomics, radiomics, radiogenomics, etc. Among them, radiomics and radiogenomics are the newer ones and are being intensively explored nowadays. The term "radiomics" was introduced in 2012 in the context of the medical imaging analysis. Medical radiomics is the computational image analysis able to extract a great number of quantitative characteristics from a particular image that cannot be obtained by the naked operator eye (21, 28). Indeed, the possibility of introducing information derived from these "omics" sciences into hybrid and/or multiscalar mathematical models are nowadays the approaches most interesting and promising with good perspectives in the diagnosis, prognosis, treatment design and follow-up of different kinds of tumors.

Traditionally, cancer was treated mainly as a genetic-disease, looking for genomic molecular targets. Genomics and proteomics are helping very much in this sense. But nowadays it may be more adequate to consider cancer as a tissue-disrupted disease. Tumor cell heterogeneity and transient tumor responses frequently lead to treatment resistance, a real dilemma in medical treatment. Dynamics of tumor cell populations, micro-environmental influences, tumor ecology and Darwinian evolution laws are clue issues to focus in future research (20,12).

Although at present many tumor types can be completely cured, other ones are much more difficult to eradicate, and they would be better considered as chronic diseases. This led to the appearance of an

*Nobel Prize in Physiology or Medicine 2018; Nature Collection, 1 October 2018

adaptive therapeutic approach that must evolve in response to the temporal and spatial variability of the tumor (metronomic therapy (15). In this context, some critical factors must be taken into more account. First, to keep a stable tumor burden (lesser tumor shrinkage means lesser tissue toxicity). Second, to design treatment strategies aimed to keep the tumor quiet avoiding its progression into more aggressive grades (letting more benign chemosensitive cell populations to survive and win the competence with more aggresive chemoresistant ones). Third, with a longer disease hold, quality of life issues emerges as much more important end-points. "Do not forget, in some incurable instances, to treat the patient and not just the cancer" (35). We must not forget that, in some cases, tumor cells can even survive the patient. In this sense, the famous patient Henrietta Lacks in the forties gave us her cervical cancer cells (HeLa cells), today established as an immortal cell line that helped us with multiple posterior cancer advances in basic and translational research.

Conflict of Interest

No relationships.

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