PERSPECTIVAS

PRECISION ONCOLOGY MUST MEET SURGICAL ONCOLOGY

A ONCOLOGIA DE PRECISÃO EM ONCOLOGIA CIRÚRGICA

JOSÉ B. PEREIRA-LEAL

Ophiomics – Precision Medicine, Lisboa, Portugal

The medical literature is rife with references to a new medical paradigm of precision medicine, also termed personalized or individualized medicine. This proposes the tailoring of interventions for treatment or prevention of disease to the individual characteristic of each patient. It was a concept popularized by the former American president Barack Obama who announced a Precision Medicine Initiative in his 2015 State of the Union address[1]. Tailoring therapy to patient was not a new concept, as illustrated by tailoring of blood transfusions to the recipient and donor ABO blood group, developed early in the 20th century. This personalization is at the heart of medicine, and its principles already described in the *Corpus Hippocraticum*[2] even if only as an aspiration.

Technology is likely the culprit that is causing this sudden enthusiasm. Technological developments associated with molecular biology, and the deciphering of the first complete sequence of the human genome are making this aspiration a possibility. Next generation Sequencing (NGS), changed the paradigm of biomedical research, enabling the massive parallel measurement of multiple molecular properties such as individual-specific sequence variation, copy number and other structural variation, person- and tissue-specific gene expression, DNA methylation, single-cell genomics and transcriptomics, etc. All this information has accumulated in public databases in vast and ever-increasing catalogues associating molecular variation with phenotypic variation in health and disease, feeding the development of new drugs, new diagnostics and rapidly translating to the clinical practice[3].

In no area like oncology have genomic technologies, and NGS in particular, had a stronger impact, nor has the notion of precision medicine shined so brightly. Genomic-changes drive cancer onset and progression, and oncology was a major emphasis of the Precision Medicine initiative of the NIH[4]. The development of targeted therapies and the stratification of patients according to the cancer biology, captured by an analysis of specific biomarkers, is becoming the norm in clinical research and clinical practice. In fact, novel cancer taxonomies have been proposed based solely on the molecular characteristics of the tumor, i.e. ignoring the organ of origins of the tumor[5-6], and the notion of organ-agnostic therapy is becoming increasingly popular[7-9]. An example of such an approach is the use of the ERBB2/HER-2-directed drug Trastuzumab in subsets of breast cancers and of gastric cancers that have an amplification/over-expression of this gene[10].

Organ-agnostic approaches only make sense, however, when considering pharmacological interventions, the realm of Precision Oncology.

What about the surgical oncology, the mainstay of primary, curative interventions for solid tumors? Molecular selection methods have not yet gained much traction in patient selection, risk stratification, guiding surgical decision-making and tailoring follow-up strategies. But as Blake Cady, former president of the Society of Surgical Oncology remarked in a speech to the society in 1996: "*In the world of surgical oncology, Biology is King, Selection is Queen, Technical maneuvers are the Prince and Princess. Occasionally the prince or princess tries to usurp the throne; they almost always fail to overcome the powerful forces of the King and Queen*[11]". Cancer is a disease driven by genomic alterations, and it is in genomic data and genomic approaches that we are likely to find the biomarkers that will enable Precision Surgery to fulfil its promises of maximizing therapeutic effectiveness, surgical safety, minimizing invasiveness and making the whole procedures and follow up more predictable, thus empowering surgeons in the pre-operative evaluation and clinical decision[12].

Biomarker-informed surgical oncology will become a reality only when surgeons take the reins of precision oncology and engage in collaborative research with genomics and bioinformatics researchers. Only surgeons can make explicit the full landscape of surgical decisions in oncology and help in mapping and evaluating them against candidate biomarkers. This will not happen on the initiative of the current Precision Oncology actors, completely focused on matching biomarkers and drugs. My own example, I hope, will be informative. I am a bioinformatician, and a few years ago, I was working with oncologists and pathologists on biomarkers in breast and esophageal cancer. Mutual acquaintances introduced us to hepatobiliary surgeons that were seeking to improve patient selection for liver cancer surgery. Dr. Hugo Pinto Marques (Lisbon Reference Centre for Hepatic Transplant) introduced me to a new world of liver transplantation in hepatocellular carcinoma (HCC), and we have been collaborating ever since. The first result of our collaboration is a gene-expression signature and algorithm for patient selection for liver transplantation that is now in prospective clinical trial (NCT04499833) and undergoing extensive multi-cohort validation. As in drug development, most biomarkers will not reach clinical use, failing testing in additional cohorts or when tested prospectively. So, we may still fail in this endeavour. However, as our collaboration with this surgical team developed, we learnt about other decisions that required biomarkers. We developed and are now validating several additional biomarker-based solutions for precision (liver) surgery. I believe we exemplify a collaboration between surgeons and bioinformaticians/genomicists that must become the norm. My aim in writing this editorial is to encourage surgical teams, in particular those involved in surgical oncology, to become the drivers in this "revolution" of biomarker-informed precision surgery.

REFERENCES

1. 2015 State of The Union Address by President Barack Obama 2015.
2. Konstantinidou MK, Karaglani M, Panagopoulou M, Fiska A, Chatzaki E. Are the Origins of Precision Medicine Found in the Corpus Hippocraticum. Mol Diagn Ther. 2017;21:601-606.
3. Malone ER, Oliva M, Sabatini PJB, Stockley TL, Siu LL. Molecular profiling for precision cancer therapies. Genome Med. 2020;12:8.
4. Collins FS, Varmus H. A new initiative on precision medicine. New England journal of medicine. 2015
5. Garraway LA. Genomics-driven oncology: framework for an emerging paradigm. J Clin Oncol. 2013;31:1806-1814.
6. National RCUSCOAFFDANTOD. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. 2011
7. Janiaud P, Serghiou S, Ioannidis JPA. New clinical trial designs in the era of precision medicine: An overview of definitions, strengths, weaknesses, and current use in oncology. Cancer Treat Rev. 2019;73:20-30.

8. Tsimberidou AM, Fountzilas E, Nikanjam M, Kurzrock R. Review of precision cancer medicine: Evolution of the treatment paradigm. Cancer Treat Rev. 2020;86:102019.
9. Yan L, Zhang W. Precision medicine becomes reality-tumor type-agnostic therapy. Cancer Commun (Lond). 2018;38:6.
10. Oh DY, Bang YJ. HER2-targeted therapies – a role beyond breast cancer. Nat Rev Clin Oncol. 2020;17:33-48.
11. Cady B. Basic principles in surgical oncology. Arch Surg. 1997;132:338-346.
12. editors. Precision in liver surgery. Seminars in liver disease 33(03); 2013; Thieme Medical Publishers; 2013.

Correspondência:
JOSÉ B. PEREIRA-LEAL
e-mail: jleal@ophiomics.com

Data de recepção do artigo:
13/03/2021

Data de aceitação do artigo:
27/07/2021