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Promises and challenges of (Immuno)Oncology

Introduction

Remarkable progress in the field of cancer research and therapy has been made in the recent years. Nonetheless, cancer holds the very sad record of being the second leading cause of death worldwide (with approximately 9.6 million deaths in 2018) and the first leading cause of death in high-income countries, being responsible, in this latter case, for twice as many deaths as cardiovascular disease [1,2].

Therefore, to date, cancer treatment remains a top-priority unmet medical need to be addressed. Luckily, pharmacological research (r)evolution, driven by scientific advances in cancer immunology, the digital revolution and the development of the patient's new role in research and care, has already started. Some of the latest trends in cancer research and development will be discussed in more detail below.

Immuno-Oncology drug development: a 2018 snapshot

From a biological point of view, cancer defines a group of cells with a non-controlled capacity to multiply and spread to new sites in the body. However, for a cancer patient it means standing up to a long and frightening uphill battle. Cancer therapy has always been a target for the phar-

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maceutical industries, which today more than ever, are significantly investing in their anti-cancer pipeline. Over the past 4 years (2014-2018) we have seen an unprecedented growth in the landscape of anti-cancer compounds, allowing 57 drugs being launched for 89 indications across 23 different cancer types[3].

Historically, the cancer treatment landscape has been characterized by waves of stunning innovations: from chemotherapy (e.g. alkylating agents, antimetabolites, taxanes, etc), to targeted therapy (e.g, imatinib, trastuzumab, etc) to immunotherapy (e.g. ipilimumab, nivolumab, pembrolizumab, etc) till the recent development of the CAR-T cell therapy. Perhaps the most exciting developments, or at least those that nowadays occupy a prominent position in the cancer treatment landscape, are the immune-related compounds. Indeed, together with chemotherapy, surgery and radiation, oncologists have now a new (in some cases more efficient) treatment option to offer to patients: cancer immunotherapies, recognized with the 2018 Nobel Prize in Physiology or Medicine. The concept of exploiting the patient's own immune system to fight cancer is not new. Indeed, Dr. William Coley, who lived in the late 19th century, can be considered one of the founding fathers of immuno-oncology. Back in 1891, he linked severe infection (so-called Coley's toxins) to regress of inoperable cancers[4], including head & neck sarcomas that nowadays is one of the most resistant cancers to checkpoint inhibitors. Coley's intuition and observations can be explained by the recent observation that some types of cancer are sensitive to an enhanced immune system. However, at that time, the poor understanding of the mechanisms underlying the observed anti-cancer effects drove oncologists to continue favoring more traditional treatments, such as surgery and radiotherapy, over immunotherapy. We are now witnessing a new dawn of cancer immunotherapy.

The research community and pharmaceutical companies are investing on drug discovery, target validation and tests, a significant part of their internal and external resources. Indeed, the current global immuno-oncology drug development pipeline includes roughly 3800 active compounds towards approximately 460 biological targets[5]. In terms of clinical trials, more than 5000 active trials, testing pipeline's drugs, are listed on the ClinicalTrials.gov registry as of August 2019[5].

The term cancer immunotherapy refers to a growing number of therapeutic protocols that aim at stimulating the patient immune system to attack the tumor. Presently, the use of inhibitors targeting immune check-

point proteins and the adoptive cell therapy CAR-T (Chimeric Antigen Receptor T-cell) are the two strategies at the forefront of the cancer "immuno-revolution" (*for more details, see box1*). Although we are at a time of remarkable changes in cancer care, these immunodrug-based treatments have still important drawbacks. To mention a few, immunotherapy is not effective in the treatment of all cancer types. Additionally, even among patients with the same cancer type, clinical data have shown very different outcomes. Last, but not least, some patients experience mild to life-threatening immuno-drug related side effects. Although there are contingency plans to clinically resolve these important side effects, drug effectiveness and reduction of potential risks are the two areas that need to be investigated in depth in the near future.

Biomarkers

Biomarker tests are becoming important tools in (i) cancer diagnosis, (ii) therapy selection and (iii) prediction of treatment response. Cancer biomarkers are currently used in clinical oncology practice either because in-label indications of an approved therapy or because they significantly contribute to clinical decision-making. As a result, biomarkers have contributed to the steady shift from the traditional "one size fits all" approach to a personalized one, where each patient is treated with the therapy that is predicted to be most effective for him/her. In the last decade the "omics" fields (genomics, transcriptomics, proteomics, epigenomics and metabolomics) and technologies (next generation sequencing and mass spectrometry) led to the rapid discovery of many biomarker candidates. Nevertheless, only a surprisingly limited number of them have made the transition to the clinic. As an example, despite the validation of a few promising immunotherapy-related predictive biomarkers, PD-L1 expression levels is presently the only approved biomarker for the stratification of patients that are likely responders to immune checkpoint inhibitors[6]. Knowledge-based challenges (e.g. cancer biology, the cancer heterogeneity, multidisciplinary skills, etc) as well as technical challenges (e.g. reproducibility, validation and reliability of the tests, data analysis, costs, accessibility, etc) make the journey of biomarkers to the clinic still long and complicated.

Developing strategies to overcome these limitations, will tremendously impact diagnosis, monitoring and treatment of cancer. This may ultimately help converting this fatal disease into a chronic, manageable condition.

Speeding up clinical trials: the seamless strategy

While science and technology are moving fast, the clinical evaluation of safety and effectiveness of an investigational drug remains the cornerstone of drug development. Historically, the process of bringing a new anticancer drug from the bench to the market could have taken, on average, 10 years. However, the fast pace of innovation and the urgency to provide patients with an early access to new and advanced therapies have made this 10-year timeline no longer acceptable and sustainable. Classical clinical trials, over the last decade, have shown, on average, an important decrease of duration[3]. However, the so-called seamless/adaptive clinical trial has become nowadays very popular since in principle, it could drastically reduce the time and the costs associated with drug development, benefitting both industry and patients. The idea behind this type of trial stems from the usage of accumulating data from the ongoing trial to modify some aspects of the study (e.g. early stop of the trial, addition/removal of treatment arms, size re-estimations, dose escalation/reduction and so on). In simple words, a seamless clinical trial addresses objectives/endpoints which are traditionally answered in separate trials. Pembrolizumab, a monoclonal antibody that binds and locks PD-1 (*see box1*), can be considered the first and the best-known example of a highly effective drug developed by a seamless approach. Back in 2011, Merck initiated a first-in-human trial to determine the safety and the dosage of pembrolizumab, in patients with advanced solid tumors. When early results showed significant response rates and durations, the sample size was significantly increased and new cohorts were added, resulting in the enrollment of more than 1200 patients[7]. Only 3-4 years after this trial was initiated, the data obtained served as the primary evidence for the accelerated approval for the use of pembrolizumab in melanoma. Given the pembrolizumab development program was so efficient, many companies have started to opt to design and conduct trials in oncology that are based on a seamless approach.

Nonetheless our belief is that the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) still prefer the classical trial when evaluating whether or not authorizing the access to the market of new drugs, both agencies, EMA first in 2007[8] followed by FDA in 2010[9], recognized the importance of these seamless-type of trials, issuing guidelines to provide industry with crucial insights on how to perceive, plan, conduct and analyse a seamless clinical trial.

While the number of seamless designs by pharmaceutical companies has risen, at present, the lack of consolidated experience on whether, when and how to prefer a seamless design to a traditional one represents a big challenge for statisticians, scientists and regulators. Ideally, a well-thought seamless design enhances flexibility and efficacy of a clinical trial, increasing its chances of success. However, there are potential concerns about those type of trials. First of all, patient safety. The lack of robust safety information might expose patients to avoidable drug-related risks since unexpected results are unlikely to be identified by the rapid, therefore limited, interim data analysis. Another potential pitfall stems from a missing or ill-defined pre-planned statistical analysis that may undermine the time- and resource-saving core concepts of the seamless clinical trial. Lastly, adaptive trials place a strong operational burden for all the parties involved: sponsor, clinicians, clinical trial sites and regulatory agencies, that need to build up solid infrastructures, procedures, training and experience, to be able to quickly respond to trial challenges.

Box 1. The Immuno-revolution

Immunotherapy is conceptually very simple. It is based on turning the body own defenses against cancer. The immune system is usually quite good to seek out and destroy invaders. However, it is less effective, or not at all, when it comes to cancer. Cancer immunotherapy deals with this issue. Two main players are leading this revolution, Chimeric Antigen receptors T-cell (CAR-T) and Immune Checkpoint Modulators.

Adoptive Cell Therapy (CAR-T): Adoptive Cell Therapy (ACT) is generated by a process by which the patient's own T cells are drawn from a patient's blood and genetically reprogrammed to recognize and target antigens selectively expressed on cancer cells. On August 27, 2018 the European Commission granted the marketing authorization of the first two cell-based advanced-therapy medicinal products in Europe. Kymriah (from Novartis) and Yescarta (Gilead sciences) are indeed two CAR-T cell therapies indicated for the treatment of pediatric and young-adult patients (up to 25 years of age) with B-cell ALL and B-cell lymphoma respectively. While CAR-T represents another important milestone achieved in the fight against cancer, it brings along crucial post-authorization safety and efficacy concerns as well as regulatory and economic challenges. This latter indeed, just few days upon EU CAR-Ts' approval, was among the top reasons that brought the National Institute for

Health and Care Excellence (NICE) to issue a draft guidance recommending against the use of Yescarta in the National Health Service. Indeed, while the NICE committee agreed on the good response rates observed in patients with untreatable forms of blood cancer, they said Yescarta is too expensive to justify its use on the UK tax-funded health service. The list-price war just started and as in every respectable role-playing, there will be some room for negotiation to bring down the costs. Of note, in Italy, on August 2019, the Italian Medicines Agency (AIFA) has given the green light for the reimbursement of the CAR-T therapy Kymriah that can now be prescribed. We hope this is just the start and one day soon CAR-T therapy will be widely available and accessible to everybody who needs it.

Immune Checkpoint Modulators: Under physiological conditions, immune checkpoints are crucial for preventing autoimmunity (self-tolerance) as well as for protecting tissues when the immune system is fighting a pathogen. The activity of the immune system (T cell response) is fine-tuned by multiple co-stimulatory and inhibitory interactions. Interestingly, inhibitory ligands and receptors that regulate T cell activity (efficacy) are commonly overexpressed on tumor cells. The two immune receptors that have been mostly studied in the context of cancer-targeted immunotherapy, are the CTLA4 and PD-1 inhibitory receptors. The Bristol-Myers Squibb Ipilimumab, a fully humanized CTLA4 antibody, was the first therapy to demonstrate a survival benefit and long-term survival in patient with metastatic melanoma, receiving the FDA approval back in 2011 for metastatic melanoma treatment. While the clinical success of Ipilimumab paved the way to new therapeutic strategies based on modulation of immune checkpoint pathways, still some patients did not benefit from anti-CTLA4 immuno-therapy. However, this was not surprising since we know that cancer cells use multiple immune checkpoints modulator to escape the immune system surveillance. As usual, the more science progresses the more are the chances to get crucial insights on cancer treatment. Yesterday was CTLA4 turn; today PD-1 (or its ligand) is in the spotlight. Tomorrow possibly, some other immune-checkpoint proteins or pathways (alone or in combination) will be targeted. Immune Checkpoint Modulators strategy strongly relies on the expression of the ligand by the tumor cells. We need to keep in mind, however, that there are several immune checkpoint pathways that impact on T-cell activity. Where are we now? Different approaches are being tested including combinatorial strategies (e.g. chemotherapy and immune checkpoints modulators). This is just one example of several combinations that are today in trial. Despite this significant progress the field suffers from the lack of reliable biomarkers, allowing clinicians to select (exclude) patients who are likely (unlikely) to respond to immunotherapy's treatments.

The rise of Artificial Intelligence & Real Word data in healthcare space

The recent mass adoption of new (high-throughput) technologies, real word data and real word evidence -embedded in the digitalization era- have flooded the healthcare space with data. Indeed, nearly 90 percent of the data ever generated has been produced over the past few years[10]. As the data volume keeps increasing, the need to make sense of it becomes crucial. If the human brain could manage to access, integrate and analyse all the health-related data out there, and then use the output to make educated guesses, answers to questions such as "What is the best treatment for this type of patient? Does the treatment work for this patient given his/her genetic background, comorbidities, life style? How does a drug that performed well in a clinical trial actually performs in the real word?" could be addressed. However, while this might sound a long way off (if not an impossible task for a human being), approaches based on Artificial Intelligence (AI) might turn out to be effective. That's not surprising since AI is able to perform repetitive tasks and in real-time analyse vast amounts of data, look for patterns and provide hypothesis to test. AI is nowadays integrated in several business sectors, but in the healthcare industry, it has the potential to truly be a life-changing player. AI applications are indeed reshaping different health sectors. Drug development is one of this. We have AI algorithms ranging from the discovery of small drug-like molecules to the identification of drug-sensitive pathway(s) or target(s), to the optimization of drug synthesis[11] till clinical trial design and patient identification for clinical trial recrutiment[12,13,14]. Diagnosis can also benefit from approaches that take advantage from AI and regulatory agencies, over the past couple of years, have shown an increasing interest. In April 2018, FDA approved the marketing of the first AI-algorithm able to identify diabetic retinopathy without clinician involvement by automatic image processing[15]. Shortly thereafter (May 2018), FDA granted marketing authorization for an AI software that aids doctors in diagnosing wrist fractures[16]. Cancer diagnostic is another big area where AI is gaining momentum. Now we have algorithms able to recognize dermoscopic melanoma[17] or classify skin cancer[18] as well as algorithms able to accurately detect lung cancer from scans[19]. This is impressive if we think that those algorithms are as good as (or sometimes better than) physicians in tackling diagnostic challenges.

One important limitation of such algorithms is that they are anchored to

previous cases, meaning that the training data sets are "small" and static and therefore might not be representative or widely applicable to most of the patients. The ability of algorithms to incorporate real-world data might represent one way to overcome this issue. In April 2019, FDA started to work on developing policies to regulate software able to real-world-learning and evolve over the time while still maintaining safety and effectiveness[20,21].The release of an FDA exploratory whitepaper demonstrates that the agency recognizes the true AI potential and it is willing to look for approaches to regulate it. While all of this is very exciting, still some important issues need to be addressed. The storage, management and integration of the heterogeneous data that is being accumulated is one of them. Data protection is definitely another one. Moreover, fully relying on AI to define the best possible treatment to deliver to patients might pave the way for ethical problems. What if, an AI-based diagnosis is wrong? Who is going to take the responsibility? Finding the best answer to these two simple questions might take years.

In principle, AI is a great and very powerful tool, but it must be validated carefully. Doctors need always to be able to answer critical questions including: AI recommendation is reasonable? Is it safe? Why AI recommended that therapy? Which path did AI take to arrive to that conclusion? Being in control of these aspects becomes even more important considering the recent failure of the IBM Watson supercomputer that recommended unsafe and incorrect cancer treatment[22]. AI technologies have definitely an important role to play in the development of health care. However, still lot of work has to be done to find a way to utilizing safely and securely patient data, with the goal to provide to caregivers tools and resources to the benefit of all.

The patient

All the breakthroughs we have seen in science and technology as well as all the changes and challenges pharma companies and regulatory agencies are facing these days, do have a lowest common denominator: patients' sake. The active participation of patients in their health and healthcare has shown to improve numerous patient's aspects outcome: care experiences, quality of life and in some cases, the match between costs and quality of service delivered[23]. However, a text-book answer to the simple question about what patient engagement is and how we do define engage-

ment, might be hard to get and can vary from person to person. What is widely recognized and accepted is that patient's engagement is a crucial aspect to advance health and healthcare. Still, patient engagement remains the Holy Grail pharma and patients' associations are seeking. Excluding those, less than 5% of adult cancer patient, that enroll in cancer clinical trials, the "journey" of a patient upon cancer diagnosis is arduous and uphill. Indeed, from diagnosis, patients need to start to process a large amount of information (not easy to retrieve), take an active role in coordinating their care by navigating and trying to orient into the not-always linear healthcare system while going through emotional and physical distress. Nowadays, doctor-patient interaction is no longer limited to 15 minutes visit in the doctor's office. Usually, whenever possible, patients either autonomously or with the help of non-experts look for more. This actually highlights patients' attitude to be better involved in different aspects of their care, including the decisional ones. That's not completely new for both the American and European regulatory agencies that already in 2016 set up a cluster with the goal to exchange experiences and best practices on how to involve patients throughout the lifecycle of a medicine[24]. The most evident added value of dragging patients into regulatory decisions stems from the fact that they bring needs and real-life experience.

While we all agree that patient engagement is a must, there is still a lot of work to fully see the benefits derived from patient engagement in the context of health and healthcare. Indeed, as with everything, patient engagement comes with downsides. The most serious concern is the possibility that the patient disagrees with the doctor's option. This would not necessarily be a bad thing if the patient's disagreement is based on trustable source such as peer-reviewed scientific publications. However, we are leaving in an era where there is an unjustified skepticism toward science, where fake news does very often hide real news. Therefore, there is a real possibility that questioning doctors' opinion would at the end just result in wasting physician's time. Time that can actually be used more effectively by asking questions, by collecting information, learning about the disease and getting involved in decisions. Lack of time indeed, seems to be one crucial problem. If patients could have access 24 hours a day, 7 days a week to a doctor, this issue would probably stop existing. Luckily, technology can play an important role in this. Smartphones, wearable devices, social media and cloud-based platforms can help managing people's health by offering support, help retrieving correct and easy-to-understand infor-

mation and identifying "signals" might speak for a doctor visit. However, the prerequisites to make this active approach work, is the building of mutual trust between patients and caregivers as well as the generation of "supervised" tools/platforms able to extend the 15-minutes visit into an on-demand one. Equipping patients with the tools necessary to take an active role in their health will ultimately lead to better health outcome and reduced healthcare costs.

Conclusions

The four aspects we briefly went through in this essay come along with significant management, business and ethical implications. However, this is how progress works and if it does, if we do progress all these areas, the ultimate winners will be the patients.

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