Editorial

Cancer in 2019 – Progress and Challenges – A Perspective

Wee Joo Chng, [1,2,3]*MB ChB, PhD, FAMS*

Patients with cancer today are doing better than they ever have been in the past. Survival rates are higher; and survival time is longer for most cancers. The drugs and treatment are getting more effective with less toxicity. Supportive care is also getting better. So, patients are not just surviving longer but also living better with good quality of life. Through effective preventive measures and screening programmes, some cancers have even seen a reduction in incidence (for example, smoking-related lung cancer and hepatitis-related hepatocellular carcinoma). Indeed, cancer is no longer a death sentence for most, and some declare that it is the new chronic disease.[1]

In fact, the outlook continues to be rosy. In terms of the understanding of cancer biology and therapeutics, significant advancements are being made. A couple of years ago, immunotherapy was hailed by Science magazine as the scientific breakthrough of the year.[2] In 2018, the Nobel Prize for Medicine was awarded for work on immune checkpoint inhibitors.[3] These immune-based treatments harness the patient's immune system to eradicate tumour cells. The mechanism of the antitumour effect is different from traditional chemotherapy and small molecule inhibitor of signalling pathways (so-called targeted therapies), providing an important addition to the anticancer armamentarium that could potentially overcome resistance to chemotherapy and targeted therapies.

The Science magazine scientific breakthrough for 2018 is for single-cell analysis[4] which has allowed unparalleled insights into the heterogeneity of tumours and the microenvironment in cancer. The ability to study genetics at the single-cell level provides insights into the evolution of tumour cells and the composition of the tumour and its microenvironment, thereby allowing us to understand the clones that survive treatment and which are responsible for relapse. This type of technological precision and scientific advancement—coupled with the unparalleled spectrum of therapeutics targeting different aspects of cancer biology that are available today—offers real opportunity for precision oncology, where specific treatment can be tailored to provide maximal benefits to individual patients based on the biology of their cancer.[5]

With the increase in precision and breadth of biological information (genomics, epigenetics, proteomics, imaging, phenotypic data, etc.) coupled with the large array of therapeutic agents and their potential combination, we are now moving into an era of big data in oncology that lends itself to the use of artificial intelligence.[6] In the last couple of years, important studies have demonstrated the accuracy of artificial intelligence over human experts in diagnosing skin cancers, genetic defects in lung cancers and also optimal drug combinations for individual patients.[7,8]

Challenges

However, there remain significant challenges. Intra-tumoural heterogeneity and evolution result in acquisition of malignant capability of tumour cells and treatment resistance. This remains a common endpoint in most incurable cancers. In addition, these changes always seem to happen one step ahead of the therapy as they are either induced by the treatment or escape the effect of the therapy. To stay ahead, we need to have a way to visualise and assess tumour cells with relative ease and regularity. Clearly, biopsy of primary or residual tumour is not always feasible. The advance of liquid biopsy with the detection of circulating tumour cells or circulating cell-free deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) from tumour cells may be potential avenues to overcome the need for biopsy of the primary tumour. However, whether they are able to reflect the entire heterogeneity in the tumour is unclear.[9] In addition, the limit of sensitivity of the assay in the setting of residual disease may limit its use in the assessment of residual clone.

While the new advancements in scientific knowledge are exciting, it also highlights the complexity of cancer and the limitations in our current knowledge. As knowledge is vital to the development of therapeutic strategies, incomplete knowledge may be one of the key limitations in our current war against cancer. In recent years, the emergence of the

[1]National University Cancer Institute, Singapore, National University Health System, Singapore
[2]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3]Cancer Science Institute of Singapore, National University of Singapore, Singapore
Address for Correspondence:Prof Chng Wee Joo, National University Cancer Institute Singapore, National University Health System, Level 7, NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228.
Email: mdccwj@nus.edu.sg

importance of non-coding RNA in cancer biology (which some years back was considered as genomic "junk"),[10] of the immune system, the host microbiome on the immune system and the impact on tumour development and response to immunotherapy,[11] show that the knowledge base is constantly evolving. How much of the cancer universe is still "dark matter" and how significant these blind spots are remain as ongoing limitations.

Even with the knowledge that we have, we seldom profile tumours in a comprehensive manner. There tends to be an over-reliance on genomics, without an understanding of the functional relevance in a particular tumour. There is an assumption that a driver mutation (which is implied based on statistical analysis of genomic data) would always be important. Indeed, this may not always be the case.

As our knowledge is incomplete, there is a need for platforms where we can test treatment in an unbiased manner, agnostic to assumptions. The development of patient-derived xenografts[12] and oraganoid cultures[13] have provided useful platforms for such testing. The development of platforms to assess drug combinations in a rapid fashion have real clinical potential.[14] Nevertheless, good platforms for testing immunotherapy in vivo or in vitro is still challenging and lacking.

Lastly, despite great success in drug development for cancer in the last decade, this, on the whole is still quite empirical. As a result, the cost of drug development is high. The process leading to drug approval is also long. Traditional endpoints may take too long to achieve or large numbers of test subjects are needed to achieve statistical power (if the drug only benefits a subpopulation of patients). The identification of good surrogate endpoints and acceptance by regulatory agencies for drug approval would be important. The development of more adaptive trial designs[15] that incorporate biomarkers such as basket trials or umbrella studies are also potentially useful but would require acceptance by regulatory agencies for such trial designs and also a mindset change from academics and industry to collaborate rather than to compete. The recent trend to form large consortiums to tackle these issues are promising.

Challenges for Singapore

For Singapore, translating and implementing all these advances in a rationale and cost-effective manner is a significant challenge. One of the greatest challenges is managing cost of cancer care.

Early stage cancers are curable with simple, short-term treatments such as surgery, while advanced cancers are costly to treat and tend to require continuous treatment with more limited benefits. Early detection is, therefore, key. The most common cancers in Singapore—breast and colorectal—have well established screening methods and programmes. But the uptake rates for these screening are only about 30% in the at-risk population in Singapore. Raising the screening rates would be an important area that needs to be tackled.

There is concern that implementation of precision oncology will lead to higher cost. Certainly, the novel drugs and genomic techniques required are costly but these are being used today anyway (albeit in an empiric manner in most cases). If we can identify the best treatments that provide the most benefits for the individual patient each time, this will maximise the cost-effectiveness and reduce waste.

Many of the tests (for example, positron emission tomography-computed tomography [PET-CT], next generation sequencing-based genomic panels) and treatments (immune checkpoint inhibitors, proton therapy, chimeric antigen receptor-T [CAR-T] therapy) are very costly and do not benefit all cancers. As practitioners, oncologists and haematologists have a responsibility to use these assays and treatments in an appropriate way. It is our duty to educate patients and the public, rather than succumb to over-servicing just because patients ask for them. Developing an appropriate care framework for oncology is therefore critical. This is also an important aspect of keeping costs down.

The issue of costs and the overall roadmap to effectively deliver cancer care in Singapore in the coming years, while taking into consideration the progress and challenges will be tackled by the National Advisory Committee on Cancer (NACC), which has been convened by the Ministry of Health.

Conclusion

As I write this at the start of 2019, we have much to be thankful for in cancer and have much to look forward to. Challenges abound in our war against cancer that will require a concerted effort. The increase in national level collaboration between hospitals, government agencies, academics, industry and other key stakeholders to tackle cancer is gratifying and puts us in a good position to make the next leap.

REFERENCES

1. American Cancer Society. Managing Cancer as a Chronic Illness. Available at: https://www.cancer.org/treatment/survivorship-during-and-after-treatment/when-cancer-doesnt-go-away.html. Accessed on 20 January 2019.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
3. The Nobel Prize. Advanced Information. Available at: https://www.nobelprize.org/prizes/medicine/2018/advanced-information/0. Accessed on 20 January 2019.

4. Pennisi E. Development cell by cell. Science 2018; 362:1344-5.
5. Prasad V, Fojo T, Brada M. Precision oncology: origins, optimism, and potential. Lancet Oncol 2016;17:e81-6.
6. Issa NT, Byers SW, Dakshanamurthy S. Big data: the next frontier for innovation in therapeutics and healthcare. Expert Rev Clin Pharmacol 2014;7:293-8.
7. Coudray N, Ocampo PS, Sakellaropoulos T, Narula N, Snuderl M, Fenyö D, et al. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. Nat Med 2018;24:1559-67.
8. Haenssle HA, Fink C, Schneiderbauer R, Toberer F, Buhl T, Blum A, et al. Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists. Ann Oncol 2018;29:1836-42.
9. Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Cancer 2017; 17:223-38.
10. Anastasiadou E, Jacob LS, Slack FJ. Non-coding RNA networks in cancer. Nat Rev Cancer 2018;18:5-18.
11. Zitvogel L, Ma Y, Raoult D, Kroemer G, Gajewski TF. The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. Science 2018; 359:1366-70.
12. Byrne AT, Alferez DG, Amant F, Annibali D, Arribas J, Biankin AV, et al. Interrogating open issues in cancer precision medicine with patient-derived xenografts. Nat Rev Cancer 2017;17:254-68.
13. Drost J, Clevers H. Organoids in cancer research. Nat Rev Cancer 2018;18:407-18.
14. Rashid MBMA, Toh TB, Hooi L, Silva A, Zhang Y, Tan PF, et al. Optimizing drug combinations against multiple myeloma using a quadratic phenotypic optimization platform (QPOP). Sci Transl Med 2018;10. pii:eaan0941.
15. 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 2018;73:20-30.