

World Cancer Day 2019 – Don't Stop Thinking About Tomorrow

Mohamad Farid, ¹*MBBS (Singapore), MRCP (UK), MPH (Harvard)*, Han Chong Toh, ¹*MBBChir (Camb), FRCP (Edin), FAMS*

“The philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow.” Sir William Osler

World Cancer Day founded and led by the Union for International Cancer Control (UICC) is a clarion call, with multiple initiatives and campaigns, to governments, health bodies, advocacy groups, grassroots organisations, communities and individuals to conquer the world's biggest disease killer in the 21st century—so as to create a cancer-free world.

A cancer-free world—really? A common question we are asked as oncologists is whether a cure for cancer has been found or is just around the corner. Reflexively, we hear ourselves answer with a long prefix—cancer is not one but a very diverse array of very heterogeneous disease types with underlying common immortalising hallmarks.¹ On deeper reflection, there is much to be gained in framing some of the most pressing issues in cancer care today through the lens of this fundamental question.

In the 21st century, the modern approach to cancer evaluation and treatment emphasises the heterogeneity between and within cancer subtypes which we can classify much more clearly and deeply than 20 years ago. Above and beyond such fine-grained taxonomy, tumour genome sequencing and molecular pathology—currently widely available at much lower cost—are performed with growing frequency to identify targetable genetic alterations or biomarkers to guide more specific therapy—a strategy called precision medicine. Patients are unique individuals; tumours, as entities arising within these individuals, and as the direct result of stochastic events and dynamic evolutionary processes, have equally one-of-a-kind features not captured by common classification schemes based on organ site, cell of origin or histomorphology. Patients should thus be treated based on changes unique to particular individual tumours independent of histologic subtype. Such an approach forms the basis of “basket” clinical trials aiming to match patients to treatments targeting specific aberration(s) that their tumours harbour. While there have been some dramatic successes, druggable oncogenic driver mutations occur in less than 15% of cancers, while

the proportion of patients with demonstrated meaningful clinical benefit and improved survival remains low,² with significant concerns for the sustainability and feasibility of a broader more universal application.³ Have we missed the fundamental and therapeutic woods for the trees?

The number of therapeutic agents against many cancers has increased significantly. These advances have undoubtedly improved outcomes for some patients—at times very profoundly—and should certainly be celebrated. A contrarian view may be that a genuinely epochal advance would identify and successfully address the truly fundamental vulnerabilities that underpin all or most neoplastic processes, success that would reflect our consummate apprehension and mastery over malignancy by going beyond the complex genetic makeup of individual tumours to exploit elemental neoplastic dependencies universally—thus pivoting back to addressing cancer as a unitary entity. We would thus contend, controversially, that depersonalising cancer therapy—“a one size fits most” approach—would be much more transformative. The astounding developments in cancer immunotherapy in the past decade raised hopes for just such a major advance. Cancer immunoediting theory provided an elegant overarching framework to think about the immune system's complex relationship with cancer, both suppressing and abetting tumours in different contexts.⁴ Monoclonal antibodies against immune checkpoints (for which the 2 lead discoverers earned the Nobel Prize for Medicine in 2018) ushered hope for the most successful therapeutic realisation of immune oncology yet—by resetting an individual's immune system following tumour immune escape; these antibodies would unleash the body's own previously stymied T cells to target neoplastic cells. As a field across a growing number of cancers, the successes with immune checkpoint inhibitors (ICI) have been spectacular and sustained for a very long period in some patients (supersurvivors). But the majority of patients with solid tumours especially, remain resistant to ICI.⁵ The impact towards improving survival across so many cancers in such a short timespan notwithstanding, immunotherapy is not a panacea. Perhaps such an all-conquering approach will forever be out of our reach due to the inherent ontogenetic

¹Division of Medical Oncology, National Cancer Centre Singapore, Singapore

Address for Correspondence: A/Prof Toh Han Chong, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.

Email: toh.han.chong@singhealth.com.sg

diversity and evolutionary dynamism of tumours. This should not diminish the scrupulousness and rigour with which we assess the impact and potential of current paradigms, including precision medicine.

And what of cure? About 50% of all cancers diagnosed globally can be cured. A substantial percentage of haematologic malignancies and germ cell tumours, in addition to the vast majority of early stage solid tumours (in some cases needing adjuvant therapy in addition to surgery) never recur following standard treatment, commonly with combination chemotherapy, bone marrow transplantation, targeted therapy led by the original “magic bullet” imatinib and biological agents. Nonetheless, even in such cases, oncologists can be hesitant to use the word cure, given examples of late recurrences across different tumour types, rare though these events may be.⁶ The treatment of metastatic solid tumours is generally characterised as palliative, though ICI has induced durable disease remissions as long as beyond 10 years for some advanced solid tumours such as malignant melanoma. Twenty years ago, advanced melanoma was a universally fatal cancer with only months of median survival⁷ and poor treatment options. Modern day cancer immunotherapy raises the possibility of some patients with advanced cancer being cured, or at least having their disease controlled and turned into a quieter, chronic disease, allowing patients to live good quality lives for years. The challenge remains to expand the group of patients for whom these durable remissions are achieved, or at least to identify them better. The significant (if not universal) success of ICI in advanced disease raises interesting questions about its role in earlier stages of disease. For example, the success with ICI in malignant melanoma—the immunogenic solid tumour poster child—has already led to its adoption as adjuvant treatment in resected stage III melanomas. Crucially, only one of the randomised adjuvant ICI trials in melanoma mandated ICI initiation at time of recurrence in the control arm to determine if survival differed between immediate ICI for all and deferred ICI only in those who recurred.⁸

The high cost of some breakthrough cancer therapies is a source of great concern. Cancer drugs overall cost more than drugs in any other medical specialty, and ample data demonstrates the significant adverse impact of financial toxicity on patients.⁹ The world’s majority of cancer patients come from low- and middle-income countries (LMICs), and access to optimal cancer treatments remains challenging in such LMICs. Over 70% of cancers in LMICs that result in premature death can be averted with achievable measures such as prevention, screening, early detection and basic cancer treatments. Yet even such programmes, medical services and infrastructure are wanting in many such countries. The recent development and approval of tisagenlecleucel—a chimeric antigen receptor (CAR) T cell

therapy which genetically engineers a patient’s own T cells to express a specific cell surface receptor targeting CD19 (a B cell receptor protein) that induces durable remissions in the majority of refractory B-cell acute lymphoblastic leukaemias—was a huge landmark development in cancer therapy, combining gene therapy and immunotherapy to spectacular effect in a setting that was, up until then, largely hopeless. The extremely high cost of this therapy, however—USD\$475,000—raises many questions about how accessible such therapies will be. The unique strategy by the company that developed the therapy (Novartis), of charging only if patients have an initial response to therapy, does not significantly mitigate the impact of the cost on payers. The majority of patients have an initial response to therapy, but up to half of these patients will relapse within 1 year.¹⁰ Unlike the explosion of knowledge in biomarkers to predict efficacy to immune checkpoint inhibitor therapy, predictive biomarkers in T cell therapy are still nascent.⁵

Cancer care is faced with 2 towering challenges—resolving the differences within and between cancers to achieve maximal therapeutic benefit, as well as bending the cost curve in cancer treatment. Successfully addressing them, rests, above all, on the unrelenting commitment to approach cancer equally as a disease of cells and genes, as one of individuals and society.

“I am and I will” is the ‘power to the people’ tagline for World Cancer Day 2019—asking of individual spirit, motivation and responsibility for our own health. Indeed, there is so much we can do to reduce the risk of cancer—exercise more, maintain an ideal body weight, sleep enough, eat right with less red meat and preserved foods, go for recommended cancer screening, stop smoking, motivate others and spread the good word. With worldwide cancer incidence still rising and poised to be the leading cause of global death this century, international bodies, governments, academic institutions, pharmaceutical companies and other stakeholders will need to implement strong cancer control policies, effective prevention strategies and improve access of evidence-based cancer care to all who need it.

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