Cancer immunotherapy—the end of the beginning

The 1990's ushered in the era of molecular oncology and targeted therapy. But its birth was rocky. On the front page of the 3 May 1998 issue of the New York Times, Father of DNA James Watson, announced that Harvard Professor Judah Folkman would cure cancer in 2 years. Folkman and his team had identified anti-angiogenic proteins endostatin and angiostatin, which completely eradicated tumours in mice when given in combination. This made the cover story of the journal *Cell*. The highly anticipated Phase 1 clinical trials of endostatin and angiostatin started soon after. Alas, James Watson's prediction for an imminent cure for cancer was not to be. The pivotal trials did not show any meaningful clinical signal. The field of anti-angiogenesis would later flourish after this early disappointment with bevacizumab and other anti-angiogenic drugs showing broad benefit across many cancers.

At that same time, the most remarkable oncology clinical trial in history was about to happen. Imatinib (Gleevec), a BCR-ABL, c-kit and platelet-derived growth factor receptor (PDFR) tyrosine kinase inhibitor developed by Harvard clinician-scientist Brian Druker and others, was tested in a first-in-human clinical trial in 31 chronic myeloid leukaemia (CML) patients. All patients dramatically achieved complete remission, and later clinical trials validated the astounding effect of 'magic bullet' Gleevec against CML, an achievement made more remarkable for the prior belief that tyrosine kinases were really undruggable. This is still the most successful phase 1 oncology trial ever—that led to the fastest approval of an oncology drug by the United States Food and Drug Administration (FDA).

The early 21 century belongs to cancer immunotherapy. The understanding of the biology of immune checkpoints between cancer and the immune system has since led to registration approvals of immune checkpoint inhibitors across many cancers in a comparably short time. Impressive also is the discovery and growing validation of biomarkers that can define patients that respond better to immune checkpoint inhibitors starting with PDL1 expression, cancer mutations, CD8+ T cell infiltration and now beyond, including the development of a cancer immunogram. An exciting and unexpected biomarker of response to immune checkpoint inhibitors lies deep in our gut—where a favourable gut microbiome can lead to superior outcomes to immunotherapy.

Chimeric antigen receptor (CAR) T cell therapy must surely be the other landmark oncology treatment after Gleevec, inducing very dramatic complete remissions in incurable, relapsed, refractory B-cell leukaemia, later lymphoma and more recently multiple myeloma. There is also a race to find biomarkers to better select patients for T cell therapy, currently prohibitively costly way beyond the reach of many patients with terminal leukaemia, lymphoma and myeloma. There has never been any clear biomarkers to identify patients who would respond better to chemotherapy, to anti-angiogenesis treatment and—outside of oncogenic addiction—to targeted therapy. The rapid progress in the understanding of the cancer-immune-microenvironment has undoubtedly led to unprecedented clinical milestones in the War on Cancer.

In this special issue of the *Chinese Clinical Oncology* focusing on Cancer Immunotherapy, it is my great privilege to be guest editor of excellent articles by key opinion leaders from diverse specialties, and experts in their respective fields. Dr. Malcolm Brenner, a giant pioneer in cancer immunotherapy since the 1980's, when he first inserted specific genes into human T cells to create potent white cells with cancer-killing capability, gives his sweeping wisdom and perspective of this fast-moving, rapidly evolving field.

Beyond the 'hot' area of immune checkpoint inhibitors and CAR T cell therapy, this issue also explores other emerging concepts of immunotherapy such as combination with radiation therapy, oncolytic viruses, and overcoming the inhibitory tumour microenvironment with indoleamine 2,3-dioxygenase (IDO) inhibitors and other similar microenvironment modulating drugs. While rational drug combinations blaze the trail in clinical immunotherapy strategies, negative studies will always bring the field down to earth. This includes the most recent phase III trial of pembrolizumab and IDO inhibitor Epacadostat which disappointingly showed that Epacadostat did not improve survival benefit when added to pembrolizumab in a heterogenous cohort of advanced malignant melanoma. Dr. Rupert Handgretinger gives a comprehensive overview of immunotherapies for childhood cancer, indicating hope is at hand for some otherwise incurable paediatric cancers. Dr. Gilberto Lopes, Director of International Programs for the American Society of Clinical Oncology (ASCO) and Editor-In-Chief of ASCO's *Journal of Global Oncology* contributes a very important discourse on the rising cost of cancer immunotherapies, penned with his colleague George Nahas. With a greater call for universal health coverage emphasizing

healthcare as a right than a privilege, access to potentially life-saving treatments that are costly or limited is a huge and challenging issue. Asian countries like Thailand are thus aiming to build their own immunotherapy capabilities with a priority on CAR T cell therapy for leukaemia and lymphoma—a therapy still available mainly in the United States and China only.

Rebecca Dent and her colleagues fascinatingly illustrate how and why some breast cancer subtypes respond much better to cancer immunotherapy. In another very common cancer, colorectal cancer, which overall does not respond much to immune checkpoint inhibition, Dr. Dawood narrates the discovery of a high mutation subset that responds significantly, and how rational combinations might enhance anti-tumour immunity in addition to this mutational Achilles' heel.

If James Watson were asked for his view on cancer immunotherapy today—I believe he would be more measured after his too optimistic frontpage headline quote in the 1998 May issue of The New York Times. In fact, anti-angiogenic therapies that normalize tumour blood vessels are now known to favourably modulate the immune microenvironment. Still, he must surely be celebrating the truly remarkable achievements of cancer immunotherapy in producing total remissions, meaningful prolongation of survival, including super survivors living beyond 10 years who previously had only months to live, and an exponential explosion in the science and translation of cancer immunology. And this time it is not in mice but in human cancer patients.

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