Editorial

Cancer immunotherapy

Li Yan[1] and Helen X. Chen[2]

Unprecedented progress has seen made in the last decade in the field of cancer immunotherapy. The recent approval of nivolumab (Opdivo), the first anti-programmed cell death-1 (PD-1) antibody, for metastatic melanoma in Japan, marked a milestone in the rapidly advancing field of cancer immunotherapy. Nivolumab together with ipilimumab (Yervoy®), the anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody, are the first 2 drugs in the class of "immune checkpoint inhibitors" that have delivered impressive responses in patients with metastatic melanoma and renal cell cancer (RCC) as well as a variety of solid tumors. The 3-year survival rate of 22% in patients with metastatic melanoma who received ipilimumab treatment represents a marked improvement in the management of this deadly disease[1]. Even more exciting, the impressive activity of ipilimumab has already been surpassed by other more active and potentially better tolerated immunotherapies, such as anti-PD-1/PD-L1 (PD-1 ligand), and combinations of immunotherapies, such as anti-PD-1 and anti-CTLA-4[2]. The high rate of durable response to these immunotherapies, with survival benefit reported up to 10 years, raise the hope that immunotherapy may provide a cure for at least some cancer patients.

The encouraging clinical efficacy of immune checkpoint inhibitors has fueled an unprecedented level of research and development (R&D) activity and investment related to cancer immunotherapy. Currently, there are at least 7 anti-PD-1 and anti-PD-L1 therapies in clinical development. There are numerous phase III trials for a broad range of indications[3,4]. The first wave of approvals is anticipated to include treatments for melanoma, RCC, and non–small cell lung cancer (NSCLC). Impressive clinical activities have also been reported for treatments targeting head and neck cancer and bladder cancer with many more cancer types being explored. One example of the high level of competition is pembrolizumab (MK-3475), which is being developed by Merck [known as Merck Sharp Dohme (MSD) in China]. Pembrolizumab is an anti-PD-1 antibody that has taken a surprising though narrow lead over nivolumab in melanoma, with an anticipated US Food & Drug Administration (FDA) action date in October 2014, filling a 4-year development gap.

Authors' Affiliations: [1]US Chinese Anti-Cancer Association; [2]Therapy Evaluation Program (CTEP) National Cancer Institute (NCI), Bethesda, MD 20892, USA.

Corresponding Authors:

Li Yan, US Chinese Anti-Cancer Association. Tel: +1-610-213-7025; Email: ynyinternational@yahoo.com.

Helen X. Chen, Therapy Evaluation Program (CTEP) National Cancer Institute (NCI), 6130 Executive Blvd, EPN 7131, Bethesda, MD 20892, USA. Tel: +1-240-276-6106; Email: helen.chen@nih.gov.

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Due to improved molecular characterization of the immune system and advances in biotechnology, significant progresses have also been made in the development of other forms of cancer immunotherapies, including adoptive T-cell transfer, novel antibody constructs, cytokines, and cancer vaccines.

With these exciting developments, it is critical that the oncology community consider in advance how to best use its R&D resources to expedite the introduction of these ground-breaking agents into medical practice. More importantly, we must evaluate how to best select the correct agents and the most appropriate regimen, including the treatment duration and combination, and how to identify candidate patients to maximize the risk/benefit ratio and have the best healthcare economic effect. In this issue of the *Chinese Journal of Cancer*, we invited thought leaders in the field of cancer immunotherapy, including Dr. James Allison, who discovered CTLA-4, to share their insightful views[5].

We would also like to share our perspectives in the following areas pertaining to different aspects of the development of cancer immunotherapy in China.

Immunotherapy for Prevalent Tumor Types in China

Several domestic Chinese companies are joining the race to develop immune checkpoint therapies. These assets are still in the preclinical stage, but they are anticipated to enter the clinical stage of development between 2016 and 2017, corresponding to the same time frame in which numerous immunotherapies from multinational companies are expected to enter clinical trials in China. It may therefore be imperative for Chinese R&D organizations to strategize and concentrate R&D efforts on cancer types that are prevalent in China but that may not be the priority of multinational companies. Among the most prevalent cancer types in China, i.e., lung, liver, and gastric cancers, global development efforts are currently concentrated in NSCLC. It is therefore expected that, in China, NSCLC will be among the first indications for immune checkpoint inhibitors to be developed by multinational companies. On the other hand, multiple phase I clinical trials on treatments for gastric cancer have been reported. Currently, 2 phase I/II trials are underway in gastric cancer (e.g., nivolumab in combination with ipilimumab and pembrolizumab as a single agent). For liver cancer, there are very few data available, with only 1 phase I study of nivolumab and 2 phase I/II studies of tremelimumab (anti-CTLA-4). Other cancer types of particular importance in China include esophageal and nasopharyngeal cancers, both of which involve viral etiology and an inflammatory

component that may potentiate sensitivity to immunotherapy. It is therefore conceivable that Chinese domestic companies may gain an advantage in developing treatments for certain indications, such as gastric, liver, esophageal, and nasopharyngeal cancers through well-focused and prioritized development efforts.

Tailoring Immunotherapy in China

A significant majority of future immunotherapies will be administered in combination with various standard-of-care agents, whether concurrently or in sequence. It is important to consider how to best integrate these promising immunotherapies into clinical practice, taking into consideration any unique features of Chinese patients. For example, the FOLFOX4 (infusional fluorouracil, leucovorin, and oxaliplatin) regimen for liver cancer was approved in 2013 in China[6]. This regimen is currently only being used in Asian patients, but it is poised to become a mainstream treatment option. Therefore, it will be prudent to plan for dedicated clinical trials to evaluate its efficacy in combination with immunotherapy in liver cancer patients. Similarly, apatinib, an inhibitor of vascular endothelial cell growth factor receptor 2 (VEGFR-2), has shown promising activities in gastric cancer and is anticipated to gain regulatory approval in China in 2014[7]. This orally administered small-molecule agent is expected to become an important component of gastric cancer treatment; however, its use will be initially limited to China. A carefully devised combination strategy in the most appropriate patient segment and treatment setting is required.

Although these immune checkpoint modulators have shown acceptable safety profiles based on the available clinical data outside of China, autoimmune diseases, including fetal cases of immune-mediated pneumonitis, are among the risks associated with this new class of medicines. It is unknown whether the toxicity profiles of various immunotherapeutic agents might be different in the Chinese patient population.

Another important consideration is the expense for the healthcare system. At the moment, the large majority of these immune-modulating agents are biologics associated with high costs.

Treatment dose and schedule

Because immune-modulating agents do not directly target tumor cells, determining the biologically optimal dose is a complex issue. For example, three dosing schedules of pembrolizumab, 2 mg/kg (n = 146) administered every 3 weeks, 10 mg/kg (n = 168) administered every 3 weeks, and 10 mg/kg (n = 51) administered every 2 weeks, have been carefully tested in patients with melanoma. Although a numerically higher response rate was observed with the dose of 10 mg/kg administered every 2 weeks, large randomized trials are required to confirm the difference, if any, in survival[8,9].

Treatment duration

The duration of therapy with checkpoint inhibitors is more or less arbitrary, ranging from 4 cycles (ipilimumab) to 1–2 years (anti-PD-1/PD-L1 antibodies), or even indefinitely while patients continue to derive treatment benefits. Prolonged responses have been observed in patients receiving only a short course of ipilimumab[1]. Emerging clinical data suggest that these agents have the potential to overcome the problem of tumor "immune adaptation" upon re-treatment of patients whose disease relapsed after initially responding to immunotherapy[10]. Given the unknown long-term safety profiles of these immune-modulating agents, it is imperative to further explore the optimal duration of treatment to maximize the benefits, while minimizing the risks, including auto-immune diseases.

It is further anticipated that the optimal duration and dose schedule may vary depending on the disease context, e.g., lung cancer may require a different treatment regimen than melanoma. Developing markers for assessing the pharmacodynamic effects, monitoring the immune response, selecting patients, and tailoring the treatment will be essential for the success of these new treatment modalities.

Immunotherapy Beyond Checkpoint Modulators in China

In addition to the immune checkpoint modulators, there are many other immunotherapeutic approaches with the promising potential for high efficacy, including long-term tumor remission, in cancer patients. These approaches include cancer vaccines, cytokines, and adoptive T-cell therapy[4,11]. Among these possibilities, the use of chimeric antigen receptor (CAR)-engineered lymphocytes is emerging as an attractive cancer therapy[11]. Multiple academic institutes and companies are developing CARs against a host of targets, from epidermal growth factor receptor variant III (EGFRvIII) and mesothelin to CD19, CD20, CD30, CD33, and CD138. Long-lasting responses, including complete remission, have been observed in patients receiving CAR therapy. Advances in the CAR technology platform are now extending its potential from chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL) to other hematologic malignancies as well as solid tumors. In fact, China is a leading nation in the development of these treatments, with a number of CAR programs in various development stages, including CARs against CD19, CD20, and mesothelin.

In summary, the era of cancer immunotherapy has arrived. These novel cancer treatments are expected to become the standard-of-care for more than 50% of cancers and will have a profound impact on our approaches to manage and treat cancer. The next 10 years will be an important time for the development of cancer immunotherapy. Basic, translational, and clinical researchers, together with Chinese and global pharmaceutical and biotechnological companies, can and should play a major role in developing cancer immunotherapies, especially for treating the major types of cancer that affect patients in China.

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