Editorial

Breakthrough Research in Onco-critical Care

Pradeep Rangappa, [1] DNB ✉

[1]Senior Consultant, Dept. of Critical Care, Manipal Hospital, Bangalore, India

Email: prangap939@gmail.com

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Cancer patients account for 15% of all admissions to intensive care unit (ICU).[1] New anticancer therapies and advanced diagnostic methods have led to a fall in mortality. The newest drugs in the oncology armamentarium are checkpoint inhibitors.[2] Checkpoints are molecules that down-regulate the pathways of T-cell activation and prevent the immune system from attacking normal cells. Checkpoint inhibitors are monoclonal antibodies that inhibit checkpoints of cancer cells, thus permitting an immune response against these cells. In a paper published in NEJM in 2010, Ipilimumab, which blocks Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), a checkpoint present in metastatic melanoma, was shown to improve overall survival.[3] Since then, other checkpoints have been described including programmed cell death 1 (PD-1), lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), T cell immunoglobulin and ITIM domain (TIGIT) and V-domain Ig suppressor of T cell activation (VISTA). PD-1 inhibitors include Nivolumab, Pembrolizumab and Cemiplimab have revolutionized the treatment of different cancers, including Merkel cell carcinoma, melanoma, head and neck squamous cell carcinoma and non-small-cell lung cancer. Thus, immunotherapy has become the fourth pillar of treatment after surgery, radiotherapy, and chemotherapy.

The latest form of immunotherapy involves drugs customised to each patient. One such therapy is the CAR T-cell therapy for hematologic malignancies.[4] T-cells are collected from each patient by leukapheresis and genes for chimeric antigen receptors (CARs) are integrated into their genome. The modified T cells express CARs on their surface and are subsequently reinfused during therapy. They bind to specific antigens on tumor cells, resulting in vigorous T cell activation and powerful anti-tumor responses. CAR T-cell drugs include Tisagenlecleucel, Axicabtagene, Brexucabtagene, Lisocabtagene, Idecabtagene and Ciltacabtagene.

Other examples of customised drugs include personalized anti-cancer vaccines and tumor-infiltrating lymphocyte (TIL) therapy.[5,6] Personalized cancer vaccines can be prepared from a variety of antigen sources, e.g. from resected tumors, RNA or DNA obtained from autologous tumor cells and autologous tumor neoantigens in the form of synthetic peptides or proteins. In TIL therapy, lymphocytes are isolated from a tumor sample obtained from the patient, expanded and activated, and once a sufficient number of TILs have been generated, they are infused back into the patient's body. The goal of TIL therapy is to enhance the host's anti-tumor immune response by providing a larger population of activated T cells that can specifically recognize and target cancer cells. The process of transferring modified immune cells such as TILs is known as adoptive cell transfer.

mRNA vaccine technology is also gaining popularity.[7] These vaccines range from dendritic cell (DC) based mRNA cancer vaccines, which involve the ex vivo loading of patient-derived DCs, to direct injection of mRNA into the tumor or surrounding tissue. These vaccines encode for specific tumor-associated antigens or neoantigens, which activates both cellular and humoral immune responses that suppress tumor growth and eradicate the tumor.

Breakthroughs are also taking place in diagnosis of cancer. Next-generation sequencing (NGS) is a new technology used for DNA and RNA sequencing and can analyse whole genomes for mutations in a short period of time. [8] Chemotherapeutic agents have been developed that target these genomic mutations, such as BRAF inhibitors that target the B-Raf mutation in colorectal cancer and

vorasidenib that targets the IDH1 or IDH2 mutations in gliomas.[9] Liquid biopsy (LB) is a new non-invasive diagnostic test for cancer that isolates tumor-derived entities such as circulating tumor cells, DNA and extracellular vesicles from the body fluids of cancer patients, and analysing the genomic and proteomic data contained within them.[10] This technique developed over the last decade looks to replace the traditional invasive diagnostic tests. Since blood is in contact with most of the tumors, LBs mostly involve blood sampling, although other body fluids like mucosa, pleural effusions, urine, and cerebrospinal fluid (CSF) are also analyzed.

Finally, deep learning, a machine learning algorithm that is a subfield of artificial intelligence (AI), supports automatic feature extraction and is being increasingly utilised in both cancer research and diagnosis.[11] These are deep neural networks that use multiple filters to recognise patterns within data such as images, and analyse language and genomic sequences. AI has been shown to successfully identify skin lesions as precisely as expert dermatologists, interpret mammograms for breast cancer and detect enlarged lymph nodes or colonic polyps in computed tomography images, or areas of cancer in histopathology slides of radical prostatectomy specimens. AI has also been used to detect tumor-infiltrating lymphocytes, which are prognostic factors for thirteen different cancer types including breast, lung and colorectal tumors, and also to assess the expression of tumor marker proteins such as HER2 in tissue slides and levels of the immune-checkpoint protein PD-L1 in needle biopsy specimens of non–small cell lung cancer. AI has been used in genomics to identify between 1000 and 100000 genomic mutations for each tumor sample. Genomic data available on the COSMIC database of the Sanger Center has been analysed using AI to identify more than 9 million mutations in gene coding regions from 26829 oncology papers. The risk of cancer recurrence can also be assessed using AI-driven analysis of stored samples. These initial experiences with AI show that it can improve the accuracy and efficiency of cancer diagnosis as well as reduce the burden on medical staff involved in tumor assessment. Currently, AI in oncology remains in the fledgling stage and requires substantially more images than the 1 million images available for machine training. This drawback is being overcome by technologies such as data augmentation and transfer learning. AI is set to become indispensable in cancer diagnosis.

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