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CAR-T "the living drugs", immune checkpoint inhibitors, and precision medicine: a new era of cancer therapy

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Abstract

New advances in the design and manufacture of monoclonal antibodies, bispecific T cell engagers, and antibody-drug conjugates make the antibody-directed agents more powerful with less toxicities. Small molecule inhibitors are routinely used now as oral targeted agents for multiple cancers. The discoveries of PD1 and PD-L1 as negative immune checkpoints for T cells have led to the revolution of modern cancer immunotherapy. Multiple agents targeting PD1, PD-L1, or CTLA-4 are widely applied as immune checkpoint inhibitors (ICIs) which alleviate the suppression of immune regulatory machineries and lead to immunoablation of once highly refractory cancers such as stage IV lung cancer. Tisagenlecleucel and axicabtagene ciloleucel are the two approved CD19-targeted chimeric antigen receptor (CAR) T cell products. Several CAR-T cell platforms targeting B cell maturation antigen (BCMA) are under active clinical trials for refractory and/or relapsed multiple myeloma. Still more targets such as CLL-1, EGFR, NKG2D and mesothelin are being directed in CAR-T cell trials for leukemia and solid tumors. Increasing numbers of novel agents are being studied to target cancer-intrinsic oncogenic pathways as well as immune checkpoints. One such an example is targeting CD47 on macrophages which represents a "do-not-eat-me" immune checkpoint. Fueling the current excitement of cancer medicine includes also TCR- T cells, TCR-like antibodies, cancer vaccines and oncolytic viruses.

Keywords: Cancer immunotherapy, CAR-T, TCR-T, Immune checkpoint inhibitor

Monoclonal antibodies (MoAb) targeting CD20 with rituximab, ofatumumab, and obinutumumab have led to a paradigm shift in B cell lymphoma and leukemia therapy [1, 2]. MoAbs targeting HER2 are widely used for breast cancer therapy [3, 4]. Small molecular inhibitors such as tyrosine kinase inhibitors (TKI) have become a major modality of therapy for a variety of cancers [5, 6]. The recent approval of chimeric antigen receptor (CAR) – engineered T cells targeting CD19 has opened a new era with "living drugs" for cancer immunotherapy [7–9]. The two collections of "Emerging agents and regimens for cancer therapy" and "Cancer immunotherapy: recent advances and future perspectives" summarized latest development in the therapy for different cancer types and the search for novel targets of cancer immunotherapy. Major advances in the following fields are particularly encouraging and promising.

Antibodies: more on-target and less off-tumor effects

New advances in the design and manufacture of MoAbs, Bispecific T cell engagers (BiTEs), and antibody-drug conjugates (ADCs) make the antibody- directed agents more powerful with less toxicities [1, 10–12]. Blinatumomab as the first approved CD19-targeted BiTE is being studied for induction therapy for elderly patients with acute lymphoblastic leukemia (ALL) and for incorporation into the regimens containing the CD22-targeted ADC, inotuzumab ozogamicin, in an attempt to enhance efficacy and reduce toxicities [13–15]. ADCs targeting CD30, CD33, or CD79 have been approved for clinical therapy of lymphomas and AML with the appropriate targets [16–18]. BiTEs for solid tumors are under active clinical trials [19, 20].

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Small molecule inhibitors (SMI) as targeted agents: small pills, big impact

Imatinib opened a new era of targeted therapies with oral SMIs [21]. BCR-ABL tyrosine kinase inhibitors (TKI) have fundamentally changed the therapeutic paradigm of chronic myeloid leukemia (CML) and possibly of ALL with BCR-ABL mutations in the near future [22, 23]. JAK2 inhibitors, ruxolitinib and fedratinib, are major therapy options for myelofibrosis [24–26]. Inhibitors for BCL-2, venetoclax, and Bruton tyrosine kinase, ibrutinib and acalabrutinib, are playing major roles in therapy for chronic lymphoid leukemia as well as in mantle cell lymphoma [27–30]. Recently, FLT3 inhibitors and inhibitors of isocitrate dehydrogenases (IDH1 and IDH2) significantly enhanced the armamentarium for AML therapy [31–35]. TKIs targeting a variety of oncoproteins, such as EGFR, ALK, HER2, FGFR, VEGFR, RET, MET, to name a few, have brought revolutions in the therapy of non-small cell lung cancer, breast cancer, bladder cancer, liver cancer, and renal cell carcinoma [5, 6, 36–42]. BRAF inhibitors targeting serine /threonine kinases lead to major advances in the therapy of malignant melanoma [43, 44]. PARP inhibitors and CDK inhibitors significantly expanded the weaponry for breast and ovarian cancers [45–50].

Immune checkpoint inhibitors (ICI): targeting tumor microenvironment, restoring immune function

The discoveries of PD1 and PD-L1 have led to the revolution of modern cancer immunotherapy [51]. Multiple agents targeting PD1, PD-L1, or CTLA-4 either as single agent or combination regimens are widely used as ICIs which alleviate the suppression of immune regulatory machineries and lead to immunoablation of once highly refractory cancer cells [52–55]. Recent discoveries on the immunomodulatory effects of gut microbiota shed lights on new ways in enhancing cancer immunotherapy [56].

CAR-T cells: living drugs

Tisagenlecleucel, the first approved CD19-targeted CAR-T cells, have been in clinical applications for refractory /relapsed (RR) ALL and large B cell lymphoma (LBCL) [8, 9, 57]. Axicabtagene ciloleucel is also approved for LBCL [9]. Several CAR-T cell products targeting B cell maturation antigen (BCMA) as well as CD19 are under active clinical trials for RR multiple myeloma [58–60]. Several biomarkers such as CLL-1, EGFR, NKG2D, and mesothelin are being targeted in CAR-T cell trials for leukemia and solid tumors [61–66]. Dual-target CAR-T cells and sequential or cocktail CAR-T cell trials have been shown to provide clinical benefits for highly refractory cancers [67]. Universal CARs are being engineered and universal CAR-T cells are in clinical trials [68, 69]. Recent discoveries in mechanisms for CAR-T toxicities (CARTox), such as cytokine release syndrome and neurotoxicities, suggest that prophylaxis for CARTox may not affect efficacy of CAR-T cells [70, 71]. These discoveries make it possible to preemptively or prophylactically treat and minimize CARTox [72–74].

Novel agents targeting new signaling pathways, biomarkers, and immune checkpoints

mTOR inhibitors, such as everolimus and temsirolimus, target and block a significant signaling pathway that proves vital for PI3K/AKT signal transduction [75]. New inhibitors for inflammasomes are being studied [76]. These novel inhibitors represent new families of targeted agents. Recently, tumor-associated macrophages in the tumor microenvironment are increasingly recognized to facilitate cancer metastasis [77]. One active approach in early clinical trials is targeting CD47 on the macrophage cell surface that represents a “do-not-eat-me” immune checkpoint molecule [78, 79]. TCR- T cells, TCR-like antibodies, cancer vaccines and oncolytic viruses are fueling new endeavors for cancer immunotherapy [80–83]. The CAR-T “living drugs”, small molecule inhibitors, and immune checkpoint inhibitors mark a new era of cancer therapy.

Abbreviation

CAR: Chimeric antigen receptor

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