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Current Evolution in Target Therapies for Blood Cancers

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Abstract

Target therapy represents a significant step forward in the treatment of malignant tumors. These therapies typically address to molecular pathways essential for the growth and replication of neoplastic cells. Given their peculiar mode of action, they constitute an overcoming of chemotherapy which, as known, affects both the proliferating cancer cells and normal cells indiscriminately. Thanks to the discovery and synthesis of compounds that interact with specific molecular defects, antineoplastic pharmacology is continually enriched with "cell-selective therapy". In this way, we move from a cure based on the disease to an increasingly personalized therapy. Important pharmacological targets are represented by: cell receptors, growth factors, transcription factors, signal transducers, cell cycle regulators, apoptosis modulators, angiogenetic factors, immune cells.

The use of new technologies for the molecular and cellular analysis of blood tumors has over time allowed the identification of new pharmacological targets and new anti-tumor treatment strategies. These new applications open the era of "precision medicine", which refers to the identification of cancer-specific biological features to choose tailored treatments and interventions in order to improve efficacy, reduce toxicity and ultimately improve health outcomes in our patients. Moreover, targeted therapy can be used along with chemo and radiotherapy to improve clinical response through a synergistic action.

Small molecule inhibitors

Small molecule inhibitors can pass through cell membrane and reach a lot of intra-cellular and extra-cellular targets. Tyrosine Kinase Inhibitors (TKIs) have revolutioned the treatment and outcome of Chronic Myeloid Leukemia (CML) and also Philadelphia-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL). Imatinib was the first TKI to be discovered in the setting of BCR-ABL TKIs and of target therapy. Although the specific targeting of that onco-protein, several point mutations in the BCR-ABL kinase domain have been related to the development of imatinib resistance. Second (dasatinib, nilotinib, bosutinib) and third-generation (ponatinib, asciminib) TKIs have been shown to lead to better outcomes in Ph+ CML [1]. Janus-kinase-2 (JAK2) inhibitors, ruxolitinib, fedratinib, pacritinb and momelotinib, are major therapeutic options for myelofibrosis [2]. Inhibitors for Bruton Tyrosine Kinase (BTK), ibrutinib, acalabrutinib, zanubrutinib, Phosphoinositide 3-Kinase-Delta (PI3Kδ), idelalisib and duvelisib, and B-Cell Lymphoma 2 (BCL2), venetoclax, can be efficacious in treating Chronic Lymphoid Leukemia (CLL) and Mantle Cell Lymphoma (MCL) [3]. First generation FMS-like tyrosine kinase 3 (FLT3) gene inhibitors (midostaurin) and next generation FLT3 inhibitors (quizartinib and gilteritinb) improve clinical outcomes in patients with Acute Myeloid Leukemia (AML) with FLT3 mutations. Genes encoding for isocitrate dehydrogenases 1 and 2, *IDH1* and *IDH2*, are frequently mutated in AML as in multiple types of human cancer. Abnormal histone and DNA methylation have emerged as common features of AML with *IDH1* and *IDH2* mutations and may cause altered stem cell differentiation. Recently, IDH inhibitors ivosidenib, olutasidenib and enasidenib have approved to treat AML with an *IDH1* or *IDH2* mutation. Hypomethylating Agents (HMAs) azacytidine or decitabine combined with venetoclax, constitute a practice-changing therapy in AML. Because of the synergistic activity and innovative mechanism of action, HMA plus venetoclax have been successfully used in people with newly diagnosed AML who are unfit for strong chemotherapy. The Hedgehog (Hh) signaling pathway, regulating several steps of embryonic development, can be mutated in a wide variety of cancers, included AML. Targeting Hh pathway components,

such as Smoothened, is a promising strategy for relapsed/refractory AML or for newly diagnose unfit patients. Recently, the selective oral inhibitor of the Hh signaling pathway, Glasdegib, has been approved in the USA and Europe in combination with low-dose Aracytin for the treatment of unfit patients with *de novo* AML [4].

Antibody-drug conjugates

The ability of monoclonal antibodies, Antibody-Drug Conjugates (ADCs) and bispecific T-cell engagers (BiTEs) to specifically bind a target antigen make the therapeutic antibodies more powerful with less toxicities. ADCs are lab-made immunoproteins linked to a chemotherapy drug. Among ADCs, gentuzumab ozogamicin attaches to a protein called CD33, found on most AML cells. The antibody acts like a homing signal, bringing the chemo drug to the leukemia cells. Inotuzumab Ozogamicin (Ino) targets the cell surface receptor CD22 coupled to a cytotoxic calicheamicin payload. InO is approved for adults with CD22-positive Relapsed/ Refractory (RR) B-cell precursor ALL. Polatuzumab vedotin is a first-in-class ADC targeting the B-cell antigen CD79b, a signaling component of the B-cell receptor, delivering the potent anti-Microtubule Agent Monomethyl Auristatin E (MMAE) inside the cell. It is approved in combination with bendamustine and rituximab in RR Diffuse Large B-Cell Lymphoma (DLBCL). Brentuximab vedotin is an anti-CD30 antibody conjugated to MMAE. It is approved for treatment of patients with Hodgkin lymphoma and systemic anaplastic large cell lymphoma after failure of at least one multiagent chemotherapy regimen. Belantamab mafodotin is a first-in-class B-Cell Maturation Antigen (BCMA)-target immunotherapy to be developed for the treatment of advanced RR Multiple Myeloma (MM) [5].

Bispecific T-cell engagers

Talquetamab, a Bispecific antibody (BiTE), binds G-protein-coupled receptor class C group 5 member (GPRC5D), a novel target on MM cells, and CD3, on T cells. Teclistamab is a BiTE that targets BCMA on MM cells and CD3 on T cells. Both drugs are licensed for treating adult RR MM [6]. Blinatumumab binds to both CD 19 site on B-cells and CD3 site on T cells, physically redirecting T-cells to tumor cells expressing CD19 and promoting tumor cell lysis and apoptosis. It has been recently approved for the treatment of CD19 positive B-cell precursor ALL in first or second complete remission with minimal residual disease greater than or equal to 0.1% in adults and children [7].

Chimeric antigen receptor (CAR) T-cell therapy

Starting from the idea that tumor-specific T-cells could eradicate cancer, Chimeric Antigen Receptor (CAR) T-cell therapy has been recently developed. CAR T cells mediate tumor killing by directing their activity against an antigen of interest through a single-chain variable fragment recognition domain. Tisagenlecleucel, the first approved CD19-targeted CAR T cells, have been introduced in clinical practice for RR ALL and DLBCL [8]. Axicabtagene ciloleucel is also approved for DLBCL. Brexucabtagene autoleucel is approved for patients with RR MCL and B-ALL. Lisocaptagene maraleucel is approved for adult patients with RR DLBCL after 2 or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma, primary mediastinal DLBCL and follicular lymphoma grade 3B [9]. Idacabtagene vicleucel and ciltacaptagene autoleucel are approved for adult patients with RR MM after four prior lines of therapy [10].

Conclusion

The concept and realization of targeted anticancer therapy continue to expand rapidly. The development of targeted agents has completely changed the outlook for patients with cancers such as CML, Ph+ ALL, MM and even AML, all diseases traditionally with a very poor prognosis but now associated with long-term survival. Unfortunately, there exists no single specific and totally effective treatment for cancer and successful development of effective therapies will require combination of target therapies with chemotherapy, radiotherapy, or even other targeting agents. Compared with off-target therapy, targeted therapy has lower toxicity, better tolerance and reduced hospitalization time, even if clinical experience has uncovered a wide range of toxicities due to the physiologic and functions of target drugs on or within normal cells or mediated by the targets of drug action. Awareness on the prevention and early recognition of adverse events during or after the treatment will facilitate timely intervention to optimize drug dosage, improve safety, and also reduce treatment costs. Overall, the potential success of targeted therapy in tumor control is undoubtedly superior to disadvantages, making incurable cancers into chronic diseases.

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