NEW PHARMACOLOGICAL APPROACHES IN THE TREATMENT OF ONCOLOGICAL DISEASES

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ABSTRACT

Malignant diseases are significant and growing health problem in almost all countries of the world. Besides the results achieved in reduction of morbidity and mortality in individual countries, significant progress of science and practice of oncology medicine and the application of new methods of diagnosis and treatment, cancer remains the second leading cause of death after cardiovascular diseases. The past decade has seen breakthroughs in personalized cancer medicine, where new targeted therapies are being developed which inhibit cellular proliferation and survival in tumors with certain specific oncogenic mutations. These new treatment approaches have shown progress in the understanding of the origin and pathogenesis of tumors, and offer hope for a good outcome of neoplastic diseases. In this review the idea is to present up-to-date report on these new molecular mechanisms and to identify their advantages and disadvantages from the pharmacological point of view.

Key words: antineoplastic drugs, oncology diseases, tyrosine-kinase inhibitors, cyclin-dependent kinases, monoclonal antibodies.

EXHIBITION

Melanoma is the deadliest form of skin cancer and has an incidence that is rising faster than any other solid tumor [1]. Currently, there are few effective treatments for disseminated melanoma and the median survival is 6–10 months. However, metastatic or unresectable melanoma treatment has improved considerably in the last five years since the introduction of the targeted therapy (BRAF and MEK inhibitors) and the immune checkpoint blockade (anti-CTLA4, anti-PD-1, and anti-PD-L1).

A significant advance in our understanding of melanoma initiation and progression was the discovery of activating mutations in BRAF. Approximately 40-60% of malignant melanomas have gene mutations at codon 600 of the BRAF gene (BRAF V600E, substitution of valine to glutamic acid) that result in constitutively activation of the mitogen-activated protein kinase (MAPK) pathway [2].

Targeting MEK

Trametinib (Mekinist®, GlaxoSmithKline) is the first-in-class mitogen-activated, extracellular signal-regulated kinase (MEK)1 and 2 activation and kinase activity inhibitor that targets a kinase in the MAPK pathway that plays a key role in oncogenic cell proliferation, survival, invasion, tumor angiogenesis, and escape from apoptosis (fig.1) [3].

Figure 1. Cell signaling pathways activated in myeloma cells through receptor tyrosine kinases (RTK).

MEK is a downstream effector of the protein kinase B-raf (BRAF) and its inhibition through trametinib causes decreased cellular proliferation, cell cycle arrest, and increased apoptosis [4]. Trametinib is approved for treatment of unresectable or metastatic melanoma in patients with a BRAF V600E or BRAF V600K mutation (as detected by an approved test), either as a single-agent or in combination with dabrafenib. The combination, which targets two different tyrosine kinases in the RAS/RAF/MEK/ERK pathway, trametinib and dabrafenib (Tafinlar®, GlaxoSmithKline), RAF kinase inhibitor, allows greater inhibition of the MAPK pathway, resulting in BRAF V600 melanoma cell death [5]. The most common adverse effects of trametinib include rash, diarrhea, fatigue, peripheral edema, and nausea. The prevalence of severe adverse events is similar in combination therapy and in monotherapy [6].

Targeting immune checkpoint blockade

Programmed cell death protein 1, also known as PD-1, is an immunoinhibitory receptor that belongs to the CD28 family and is expressed on T cells, B cells, monocytes, natural killer cells, and many tumor-infiltrating lymphocytes (TILs) [7]. PD-1 binds to 2 ligands that have been described – PD-L1 and PD-L2 [8]. Activation of this receptors leads to suppression of T-cell proliferation, cytokine production, and cell adhesion [9]. To avoid the destructive power of the
immune system, certain tumors upregulate expression of PD-1 ligands and this mark has been correlated with poor prognosis [10, 11]. Pharmacological approach in influencing this pathway, by which tumors escape immune response, can overcome resistance to tumors and help tumor-specific T cells to carry out their cytotoxic functions [12].

Nivolumab (Opdivo®, BMS-936558/MDX-1106, Bristol-Myers Squibb) is a fully human immunoglobulin G4(IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor in order to block the ligands PD-L1 and PD-L2 and escape binding (fig.2).

Figure 2. Approaches of immunotherapy to restore the normal function of tumor specific T-cells.

Nivolumab binds to the CTLA-4 with greater affinity than CD80 and CD86, inducing a cell-mediated immune response and breaking down T-cell tolerance to finally reduce tumor burden. It acts indirectly as enhancing of T-cell mediated immune response. In melanoma patients, the mean lymphocyte count increased in the peripheral blood throughout the induction phase depending on the dose [16]. The most common side effects are diarrhea, rash, itching, fatigue, nausea and vomiting, decreased appetite, and abdominal pain. These were mostly mild to moderate (grade 1 or 2). However, 10 to 15 percent of patients suffered severe immune-related adverse events (irAEs) of grade 3 or 4 and included diarrhea/colitis (8%), endocrinopathy (2%), dermatologic toxicity (< 2%), and hepatic toxicity (< 1%). Most irAEs resolved by 6 to 8 weeks with appropriate immunosuppressive treatment (mostly glucocorticoids), although residual symptoms (e.g., vitiligo, endocrinopathy symptoms, rectal pain) were sometimes present in long-term survivors [17].

New therapies have helped to improve the outcome of the unresectable or metastatic melanoma, but not without some drawbacks, such as low-response rate (immune checkpoint blockade) or short-term responses (targeted therapy) [18]. However, combination therapies using this agent along with other targeted therapies and immunotherapies are currently under investigation.

Chronic lymphocytic leukemia (CLL) is one of the most common leukemias in the Western world, characterized by the monoclonal proliferation of mature B lymphocytes in the blood, lymph nodes, and marrow. The median age at diagnosis is around 70 years. For patients with CLL with 17p deletion or TP53 mutation previously there have been less promising treatment options available. Recently several new chemo-free treatment options have been introduced within clinical trials.

**Targeting BTK**

Ibrutinib (Imbruvica®, Janssen) is a potent and irreversible inhibitor of Bruton’s tyrosine kinase (BTK), by covalently binding to a cysteine residue (Cys-481) in the active site of BTK. BTK is an integral component of the B-cell receptor (BCR) and cytokine receptor pathways and is important for survival of malignant B-cells (fig. 3).
The kinase inhibition with ibrutinib, this impedes the uncontrolled proliferation of malignant B-cell proliferation and survival. It is approved for treatment of patients with chronic lymphocytic leukemia (CLL, also with 17p deletion) and mantle cell lymphoma (MCL) who have received at least 1 prior therapy. Pharmacokinetic parameters of ibrutinib were rapid absorption, with bioavailability of 67% (in fasting state), volume of distribution ~ 10 000 L, oral plasma clearance ~ 1000 L/h and half-life elimination ~ 4 to 6 hours [19]. The dose used for the treatment of CLL, including 17p deletion was 420 mg p.o. once daily [20] and 560 mg p.o. once daily in MCL [21]. The most common adverse reactions in pivotal clinical trials were diarrhea, and 560 mg p.o. once daily in MCL [21]. The most common side effects of grade 3 and 4 included infections, anemia, neutropenia, and skin rashes.

Ofatumumab (Arzerra®, GlaxoSmithKline) is a fully humanized monoclonal CD20 antibody approved for treatment of previously untreated CLL (in combination with chlorambucil) when fludarabine-based therapy is considered inappropriate and treatment of CLL refractory to fludarabine and alemtuzumab. It has a new mechanism of action, which is associated with the selective binding to the “large and small loop” of the CD20 molecule, thus the action of the complement system and antibody-dependent cell-mediated toxicity, which, in turn, is greater extent destroys the malignant B-cells. The binding of the “small loop” thus differs from the binding site of the second currently available CD20 antibody rituximab. This explains the higher efficacy towards chronic lymphocytic leukemia (CLL) cells compared to rituximab [24]. In addition, ofatumumab remains longer at the binding place, resulting in a greater activation of the immune system – may be an indication for the particularly high effectiveness of the new drug, even at low levels of CD20 expression, as is the case in CLL. Ofatumumab was found to be well tolerated, some side effects that occurred in at least 10 percent of the patients included infections, anemia, neutropenia, and skin rashes.

The known under the name of BRCA 1 and 2 mutations can lead to breast and ovarian cancer in hereditary predisposed women. BRCA are tumor suppressor genes that are involved in DNA repair at the double strand, called homologous recombination. In addition, the known cell repair mechanism in the single-stranded is involved in the enzyme poly ADP-ribose polymerase (PARP).

Olaparib (Lynparza®, AZD-2281, AstraZeneca) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis such as DNA transcription, cell cycle regulation, and DNA repair. The PARPs have a particularly critical role in the BER pathway, binding to single-strand breaks (SSBs) in DNA, modifying proteins in the vicinity, and ultimately leading to the recruitment of DNA repair proteins to the sites of damage (fig.4).

**Targeting PI3Kα**

Idelalisib (Zydelig®, GS-1101, Gilead Sciences) is a first-in-class, orally administered, phosphatidylinositol 3-kinase-α inhibitor that was recently approved for the treatment of relapsed chronic lymphocytic leukemia (CLL) (in combination with rituximab) when rituximab alone is an appropriate therapy due to other comorbidities, relapsed follicular B-cell non-Hodgkin’s lymphoma (NHL) and relapsed small lymphocytic lymphoma (SLL) in the USA and for the treatment of CLL and refractory follicular lymphoma in the EU. Idelalisib selectively inhibits the binding of adenosine-5′-triphosphate (ATP) to the catalytic domain of PI3Kα, whereby the phosphorylation of key lipid second messengers phosphatidylinositol and inhibited the phosphorylation of Akt (protein kinase B) are prevented. Idelalisib inhibits also several other signaling pathways, including B-cell, CXCR4 and CXCR5 receptor signaling, which may play important roles in CLL pathophysiology [22]. In addition, the new drug induces apoptosis and inhibits proliferation in cell lines derived from malignant B lymphocytes as well as in primary tumor cells. Most common side effects in the pivotal studies of idelalisib were infections, neutropenia, inflammatory changes in the lung, severe diarrhea, intestinal inflammation, rashes, fever, increased liver enzymes, and increased triglyceride levels. Possible interactions should be taken into account as the main metabolite – GS-563117 is a potent inhibitor of CYP3A4 and drugs that are metabolized by this isoform should be avoided [23].

**Targeting CD20**

Ofatumumab (Arzerra®, GlaxoSmithKline) is a fully humanized monoclonal CD20 antibody approved for treatment of previously untreated CLL (in combination with chlorambucil) when fludarabine-based therapy is considered inappropriate and treatment of CLL refractory to fludarabine and alemtuzumab. It has a new mechanism of action, which is associated with the selective binding to the “large and small loop” of the CD20 molecule, thus enhances the action of the complement system and antibody-dependent cell-mediated toxicity, which, in turn, is greater extent destroys the malignant B-cells. The binding of the “small loop” thus differs from the binding site of the second currently available CD20 antibody rituximab. This explains the higher efficacy towards chronic lymphocytic leukemia (CLL) cells compared to rituximab [24]. In addition, ofatumumab remains longer at the binding place, resulting in a greater activation of the immune system – may be an indication for the particularly high effectiveness of the new drug, even at low levels of CD20 expression, as is the case in CLL. Ofatumumab was found to be well tolerated, some side effects that occurred in at least 10 percent of the patients included infections, anemia, neutropenia, and skin rashes.

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Cytotoxicity of olaparib may involve inhibition of PARP enzymatic activity, which induces synthetic lethality in BRCA1/2 deficient tumor cells through increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death [25]. The cells with functioning BRCA gene are not affected. Olaparib may be used as monotherapy for the treatment of adult patients with platinum-sensitive recurrence of a BRCA-mutated ovarian, fallopian tube or peritoneal cancer. It is available orally in capsule dosage form, which is administered 400 mg twice daily. Most common side effects are nausea, vomiting, fatigue and anemia.

Cellular proliferation, survival and growth are tightly controlled by the cell-cycle regulatory enzymes, serine/threonine kinases, which form complexes with cyclins. Cell cycle is composed of four phases—the S phase of DNA synthesis, the M phase of mitosis, and two gap phases, G1 and G2 [26]. There are four proliferative CDKs: CDK1 regulates the transition from G2 to M phase and CDK2, -4, and -6 regulate the transition from G1 to S phase [27]. However, CDK4 and -6 are critical drivers of oncogenesis in some tumors and therefore an attractive target for drug development [28]. Furthermore, CDK4/6 inhibitors are more efficient and less toxic antineoplastic agents than molecules targeting other CDKs [29].

REFERENCES:


Inhibition of cyclin-dependent kinases (CDKs)

Palbociclib (Ibrance®, PD-0332991, Pfizer) is a potent and selective inhibitor of CDK-4 and -6, which are critical components of the cell-cycle regulatory machinery. Palbociclib is approved by FDA in combination with letrozole, as a first-line treatment for postmenopausal women with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer who have not received previous systemic treatment for their advanced disease. The accelerated submission is based on the final results of PALOMA-1, a randomized phase II study with 165 postmenopausal women with advanced or metastatic breast cancer with (ER +)/ (HER2-) comparing palbociclib (125 mg once daily for three out of four weeks in repeated cycles) plus letrozole versus letrozole alone (2.5 mg once daily on a continuous regimen) in this population of patients. Combination therapy with palbociclib doubled disease-free survival (20.2 months versus 10.2 months) [30].

CONCLUSION

Over the past 50 years, the efficacy of cancer chemotherapy has improved considerably. However, the overall survival and other outcome parameters in metastatic cases have changed only modestly. More key molecules have been identified as targets for specific drugs due to the advanced knowledge of molecular pathways and regulatory processes within tumor cells. These could improve established therapeutic strategies, such as humanized antibodies or small-molecule inhibitors directed against growth regulatory kinases, or brand new approaches. Significant progress in this area gives hope for individualized therapy with detection of specific gene mutations, which could contribute to better outcome of neoplastic diseases. However, it takes time of these new approaches to be confirmed in clinical practice, but there is light in the tunnel.
mechanisms of interaction with PD-1. \textit{Int Immunol.} 2010 Aug;22(8):651-660. [PubMed] [CrossRef]


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