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RECENT ADVANCES IN THE DEVELOPMENT OF ANTINEOPLASTIC AGENT

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ABSTRACT

Through years of evolutionary selection pressures, organisms have developed potent toxins that coincidentally have marked antineoplastic activity. These natural products have been vital for the development of multiagent treatment regimens currently employed in cancer chemotherapy and are used in the treatment of a variety of malignancies. Therefore, this review catalogs recent advances in natural product-based drug discovery via the examination of mechanisms of action and available clinical data to highlight the utility of these novel compounds in the burgeoning age of precision medicine. The review also highlights the recent development of antibody-drug conjugates and other immunotoxins, which are capable of delivering highly cytotoxic agents previously deemed too toxic to elicit therapeutic benefit preferentially to neoplastic cells. Finally, the review examines products not currently used in the clinic that have novel mechanisms of action, and may serve to supplement current chemotherapeutic protocols.

KEY WORDS: Cancer, Bioavailability, Antineoplastic agent, FDA.

INTRODUCTION

The diversity of natural products currently used in the clinical setting to treat solid tumors, as well as disseminated cancers is truly extensive. Under the pressure of natural selection, various species produce cytotoxic secondary metabolites to combat potential predators, prey, or competition in the so-called "arms race" of evolution. Remarkably, some of these natural toxins appear to exhibit potent antineoplastic activity, and after years of research, have found their way from the ocean or soil to the highly heterogeneous environment of clinical oncology. The origins of cancer chemotherapy can be traced to human-made compounds, as Goodman, Gilman, and colleagues at Yale University began investigating the potential of nitrogen mustards in 1942, which was shortly followed by Sidney Farber's use of the antifolate aminopterin to induce remissions among children with leukemia in 1947. However, the institution of natural products and semisynthetic derivatives of these compounds in the latter part of the 20th century potentiated the idea of concomitant chemotherapy; using a variety of antineoplastic agents with different mechanisms of action to significantly perturb neoplastic development, and in some cases, produce long-term remissions.

Owing to recent advances in molecular biology, investigators have begun unraveling essential oncogenic pathways in carcinogenesis, potentiating an era of chemotherapy in which it is possible to theorize cancer-specific targets. This has launched the introduction of precision medicine in cancer chemotherapy in which clinicians now have the capability of selecting optimal therapies based on the genetic and phenotypic profile of the patient's malignancy in addition to traditional broad-spanning cytotoxic antineoplastic intervention. Despite these commendable advances in targeted therapy, natural products and their derivatives are still extensively relied upon against malignancies where finding cancer-specific targets has been less successful, and are often used in combination with these targeted approaches to generate more thorough treatment protocols. Further, novel natural product derivatives have shown notably efficacy against previously unresponsive malignancies at the clinical level, suggesting that natural product-based drug discovery still has considerable utility in the burgeoning era of personalized chemotherapy. Finally, natural products have the potential to improve novel immunotherapeutic strategies by conjugating monoclonal antibodies (mABs) or cytokines to highly cytotoxic compounds that have too low of a therapeutic index without an appropriate guidance mechanism. [Matthew Trendowski 2015]

Some recent drug aprroved by FDA (Food and Drug Administration) America

1. Erdafitnib

Erdafitinib is a once-daily, oral fibroblast growth factor receptor (FGFR) kinase inhibitor.

Erdafitnib is specifically indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC), that has:

• Susceptible FGFR3 or FGFR2 genetic alterations, and
• Progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Balversa.
Erdafitnib is supplied as a tablet for oral administration.

Mechanism of Action
Erdafitnib is a once-daily, oral fibroblast growth factor receptor (FGFR) kinase inhibitor that binds to and inhibits enzymatic activity of FGFR1, FGFR2, FGFR3 and FGFR4 based on in vitro data. Erdafitinib also binds to RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2. Erdafitinib inhibited FGFR phosphorylation and signaling and decreased cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplifications, and fusions. Erdafitinib demonstrated antitumor activity in FGFR-expressing cell lines and xenograft models derived from tumor types, including bladder cancer.

Pharmacodynamics
Upon administration, it was observed that erdafitinib increased serum phosphate level as a consequence of FGFR inhibition. Erdafitinib should be increased to the maximum recommended dse to achieve target serum phosphate levels of 5.5– 7.0 mg/dL in early cycles with continuous daily dosing.

Subsequently, in erfatinib clinical trials, the use of drugs which could increase serum phosphate levels, such as potassium phosphate supplements, vitamin D supplements, antacids, phosphate-containing enemas or laxatives, and medications known to have phosphate as an excipient were prohibited unless no alternatives existed. To manage phosphate elevation, phosphate binders were utilized. Additionally, the concomitant use of agents that can alter serum phosphate levels before the initial erfatinib dose increase period based on serum phosphate levels was also avoided.

Furthermore, based on the evaluation of QTc interval in an open-label, dose escalation, and dose expansion study in 187 patients with cancer, erdafitinib had no large effect (i.e., > 20 ms) on the QTc interval.

Pharmacokinetics
Absorption
Following administration of erdafitinib 8 mg once daily, the mean (coefficient of variation [CV%]) steady-state maximum observed plasma concentration (Cmax), area under the curve (AUCtau), and minimum observed plasma concentration (Cmin) were 1,399 ng/mL (51%), 29, 268 ng·h/mL (60%), and 936 ng/mL (65%), respectively.

Following single and repeat once daily dosing, erdafitinib exposure (maximum observed plasma concentration [Cmax] and area under the plasma concentration time curve [AUC]) increased proportionally across the dose range of 0.5 to 12 mg (0.06 to 1.3 times the maximum approved recommended dose) Label. Steady state was achieved after 2 weeks with once daily dosing and the mean accumulation ratio was 4-fold.

The median time to achieve peak plasma concentration (tmax) was 2.5 hours (range: 2 to 6 hours). And finally, no clinically meaningful differences with erdafitinib pharmacokinetics were observed following administration of a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50% of total caloric content of the meal from fat) in healthy subjects.

Volume of distribution
The mean apparent volume of distribution determined for erdafitinib is about 26 to 29 L in patients.

Protein binding
The protein binding recorded for erdafitinib is approximately 99.8%, and it was determined to be primarily bound to alpha-1-acid glycoprotein.

Metabolism
It has been determined that erdafitinib is primarily metabolized by the cytochrome CYP2C9 and CYP3A4 isoenzymes Label. The contribution of CYP2C9 and CYP3A4 in the total clearance of erdafitinib is estimated to be 39% and 20% respectively. Unchanged erdafitinib was ultimately the predominant drug-related moiety found in the plasma - there were no circulating metabolites observed.

Route of elimination
After administering a single oral dose of radiolabeled erdafitinib, about 69% of the dose was recovered in feces (19% as unchanged) and 19% in urine (13% as unchanged).

Half life
The mean effective half-life documented for erdafitinib is 59 hours Label, although it has also been observed between 50 to 60 hours. [Drug bank2019]

Side Effects
Adverse effects associated with the use of Balversa may include, but are not limited to, the following:

Phosphate increased
Stomatitis, fatigue, creatinine increased, diarrhea, dry mouth, onycholysis, alanine aminotransferase increased, alkaline phosphatase increased, sodium decreased, decreased appetite, albumin decreased, dysgeusia, hemoglobin decreased, dry skin.

2. Pembrolizumab
Pembrolizumab is a highly selective IgG4-kappa humanized monoclonal antibody against PD-1 receptor.

It was generated by grafting the variable sequences of a very high-affinity mouse antihuman PD-1 antibody onto a human IgG4-kappa isotype with the containing a stabilizing S228P Fc mutation. It contains 32 cysteine residues and the complete folded molecule includes 4 disulfide linkages as interchain bonds and 23 interchain bonds. It was developed by Merck & Co and firstly approved for the treatment of metastatic malignant melanoma. This is the first approved therapy against PD-1.2 It was approved firstly by the FDA on September 4, 2014. Its approval in melanoma was extended to several countries such as Australia, Israel, Korea, Macau, the European Union and the United Arab Emirates. On June 12, 2018, Pembrolizumab was approved for the treatment of cervical cancer under the status of accelerated approval.

Pharmacodynamics

Pembrolizumab pharmacodynamic reports indicate that there are not effector functions by binding to C1q and CD64 not by cytokine release.3 On clinical trials, the objective response rate, defined as the proportion of patients with tumor size reduction of a predefined amount for a minimum time period, was assessed based on independent central review and a response duration. These studies performed for different classes of cancer showed a response either partial or complete in a range of 14.3-26% of the individuals. The response duration was estimated to be of 11 months and 45-91% of the patients had a response equal or greater than 6 months.

In other clinical trials, it was reported the progression-free survival, defined as the time during and after the treatment that the patient lives with the disease without worsening. The administration of pembrolizumab improved the progression-free survival when compared to patients assigned to regular chemotherapy. The increase reached 34% of the individuals while chemotherapy reports only 16%.

The results mentioned above have been so clear and consistent that in phase III clinical trials the trial was stopped early to allow patients to switch to the treatment with pembrolizumab.

Mechanism of Action

Pembrolizumb, as an IgG4 subclass antibody, is preferred over other subclasses as it only induces weakly the complement and cell activation due to low affinity to C1q and Fc receptors. It binds with high affinity to the cell surface receptor programmed cell death protein 1 (PD-1) and it antagonizes its interaction with its known ligands PD-L1 and PD-L2. In normal circumstances, the binding of the ligands of PD-1 to the receptor inhibits the TCR-mediated T cell proliferation and cytokine production. This inhibitory signal seems to be essential for self-tolerance, collateral damage minimizing after immune response against a pathogen and maternal tolerance to fetal tissue. Therefore, the binding of pembrolizumab to PD-1 prevents the inhibitory pathway causing a physiological shift to immune reactivity and enhancing tumor immunosurveillance and anti-tumor immune response.

Pharmacokinetics

Absorption

When administered intravenously, pembrolizumab is completely bioavailable. When administered in repeated doses every 3 weeks, the systemic accumulation accounts for a 2.2 fold increase.3 the reported time to reach steady-state is of 18 weeks.8 The absorption profile of pembrolizumab is proportionally increased with increases in the dosage.

Volume of distribution

The volume of distribution at steady state of pembrolizumab is 7.5 L which indicated a limited extravascular distribution.

Protein binding

Pembrolizumab is not expected to bind to plasma proteins in a specific manner.

Metabolism

Pembrolizumab is catalyzed into small peptides and single amino acids via general protein degradation but it does not rely on metabolism for clearance. [Drug bank2019]

Side Effects

Adverse effects associated with the use of Keytruda may include, but are not limited to, the following: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, abdominal pain.

3. Venetoclax

Venetoclax is a BCL-2 inhibitor that was initially approved by the FDA in April 2016 Label. Proteins in the B cell CLL/lymphoma 2 (BCL-2) family are important regulators of the apoptotic (programmed cell death) process 1, 2. Venetoclax is used to treat chronic lymphocytic leukemia (CLL) and certain types of small lymphocytic lymphoma. CLL is the most prevalent leukemia diagnosed in Western countries. Venetoclax was developed through reverse engineering of the BCL-2 protein family inhibitor, navitoclax. Venetoclax is approximately 10 times more potent than navitoclax with regard to induction of apoptosis in CLL cells 7. A new indication was approved in 2018 for the treatment patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy. Previously, this drug was indicated only for patients with 17p gene deletions.

Pharmacodynamics

Venetoclax induces rapid and potent onset apoptosis of CLL cells, powerful enough to act within 24h and to lead to tumor lysis syndrome. Selective targeting of BCL2

with venetoclax has demonstrated a manageable safety profile and has been shown to induce significant response in patients with relapsed CLL (chronic lymphocytic leukemia) or SLL (small lymphocytic leukemia), including patients with poor prognostic features 6. This drug is not expected to have a significant impact on the cardiac QT interval. Venetoclax has demonstrated efficacy in various types of lymphoid malignancies, including relapsed/ refractory CLL harboring deletion 17p, with an overall response rate of approximately 80%.

Mechanism of action

Proteins in the B cell CLL/lymphoma 2 (BCL-2) family are necessary regulators of the apoptotic (anti-cell programmed death) process. This family comprises proapoptotic and prosurvival proteins for various cells. Cancer cells evade apoptosis by inhibiting programmed cell death (apoptosis). The therapeutic potential of directly inhibiting prosurvival proteins was unveiled with the development of navitoclax, a selective inhibitor of both BCL-2 and BCL-2-like 1 (BCL-X(L)), which has demonstrated clinical efficacy in some BCL-2-dependent hematological cancers 1. Selective inhibition of BCL-2 by venetoclax, sparing BCL-xL enables therapeutic induction of apoptosis without the negative effect of thrombocytopenia. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins, leading to mitochondrial outer membrane permeabilization and the activation of caspase enzymes. In nonclinical studies, venetoclax has shown cytotoxic activity in tumor cells that overexpress BCL-2.

Pharmacokinetics

Absorption

Following several oral administrations after a meal, the maximum plasma concentration of venetoclax was reached 5-8 hours after the dose 3. Venetoclax steady state AUC (area under the curve) increased proportionally over the dose range of 150-800 mg. After a low-fat meal, venetoclax mean (± standard deviation) steady-state Cmax was 2.1 ± 1.1 µg/mL and AUC0-24 was 32.8 ± 16.9 µg•h/mL at the 400 mg once daily dose.

When compared with the fasted state, venetoclax exposure increased by 3.4 times when ingested with a low-fat meal and 5.2 times with a high-fat meal. When comparing low versus high fat, the Cmax and AUC were both increased by 50% when ingested with a high-fat meal. The FDA indicataes that venetoclax should be taken with food.

Volume of distribution

The population estimate for apparent volume of distribution (Vdss/F) of venetoclax ranged from 256-321 L.

Protein binding

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 µM (0.87-26 µg/mL). The mean blood-to-plasma ratio was 0.57.

Metabolism

In vitro studies demonstrated that venetoclax is predominantly metabolized as a substrate of CYP3A4/5.

Route of elimination

After single oral administration of 200 mg radiolabeled [14C]-venetoclax dose to healthy subjects, >99.9% of the dose was found in feces and <0.1% of the dose was excreted in urine within 9 days, suggesting that hepatic elimination is responsible for the clearance of venetoclax from systemic circulation. Unchanged venetoclax accounted for 20.8% of the radioactive dose excreted in feces.

Half life

The half-life of venetoclax is reported to be 19-26 hours, after administration of a single 50-mg dose. [Drug bank 2019]

Side effects

Adverse effects associated with the use of Venclexta plus Gazyva may include, but are not limited to, the following white blood cell count, diarrhea,fatigue, nausea, low red blood cell count, upper respiratory tract infection.

4. Selinexor

Selinexor is a first in class selective inhibitor of nuclear transport (SINE) compound. It is currently approved for the treatment of multiple myeloma, a cancer which forms from antibody-producing plasma cells.[t] This condition is typically treated with high dose bortezomib and dexamethasone chemotherapy followed by autologous stem-cell transplant. Other chemotherapies for multiple myeloma include lenalidomide and dexamethasone, thalidomide, and may include melphalan if the patient is not eligible for transplant. Selinexor was approved by the FDA in June 2019. It was granted fast track and orphan designation as well as accelerated approval based on single arm, open label trial data. The Bortezomib, Selinexor, and Dexamethasone in Patients With Multiple Myeloma (BOSTON) trial is planned to finish in 2020.

Pharmacodynamics

Selinexor causes cell cycle arrest and apoptosis in cancer cells.

Mechanism of action

Selinexor binds to and inhibits exportin-1 (XPO1). XPO1 is a nuclear exporter protein which contains a pocket to which nuclear proteins can bind. When complexed with these proteins and Ran, activated through guanosine triphosphate (GTP) binding, the XPO1-protein-Ran-GTP complex is able to exit the nucleus through a nuclear pore. Once outside, GTP is

hydrolyzed and the complex dissociates. The inhibition of this process in cancer cells allows the targets of XPO1, many of which are tumor suppressors, to collect in the nucleus and result in increased transcription of tumor suppressor genes. Tumor suppressor proteins known to be affected by XPO1 inhibition include p53, p73, adenomatous polyposis coli, retinoblastoma, forkhead box protein O, breast cancer 1, nucleophosmin, and merlin. Regulators of cell cycle progression are also affected, namely p21, p27, galectin-3, and Tob. Inhibitor of NFκB also collects in the nucleus as a result leading to reduced activity of NFκB, a known contributor to cancer.4,5 XPO1 participates in the formation of a complex with eukaryotic initiation factor 4E and contributes to the transport of messenger RNA for several oncegenes including cell cycle promotors, cyclin D1, cyclin E, and CDK2/4/6, as well as antiapoptotic proteins, Mcl-1 and Bcl-xL.4 These wide ranging changes in protein expression and gene transcription culminate in cell cycle arrest and the promotion of apoptosis in cancer cells.[Drug Bank 2019]

Pharmacokinetics

Absorption

A single 80 mg dose of selinexor produces a mean Cmax of 680 ng/mL and a mean AUC of 5386 ng*h/mL. This relationship is dose proportion over the range of 3-85 mg/m2 which encompasses the range of 0.06-1.8 times the approved dosage. The official FDA labeling reports the Tmax as 4 hours but phase 1 studies have found a range of 2-4 hours.L Administering selinexor with food, either a high or low fat meal, results in an increase in the AUC of approximately 15-20% but this is not expected to be clinically significant.

Volume of distribution

The mean apparent volume of distribution is 125L.Label A phase 1 study reported mean apparent volumes of distribution ranging from 1.9-2.9 L/kg in their investigation of food and formulation effects.

Protein binding

Selinexor is 95% bound to plasma proteins.

Metabolism

Selinexor is known to be metabolized through CYP3A4, UDP-glucuronosyltransferases, and glutathione S-transferases although the metabolite profile has yet to be characterized in published literature. The primary metabolites found in urine and plasma are glucuronide conjugates.

Side Effects

Adverse effects associated with the use of Xpovio may include, but are not limited to, the following: thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, upper respiratory tract infection. [Drug bank 2019]

CONCLUSION

Pharmacological activities associated with natural products have been recognized since the beginning of mankind; however only limited numbers of medicinal plants and other products have been scientifically evaluated so far. Many plant products and their chemical derivatives have been used in therapeutics of serious diseases such as cancer.

CONFLICT OF INTEREST

There is no conflict of interest.

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