Chapter 2
Clinical Anticancer Drugs for Cancer Treatment

Besides cytoreductive surgery and radiotherapy, chemotherapy is the most widely used therapeutic strategy in combating cancer. The high incidence of cancer has led to a lot of immunotherapeutic and chemotherapeutic drugs to be developed and approved by U.S. Food and Drug Administration (FDA). Antineoplastic agents (approved or under development) can be broadly classified into:

(1) Antimetabolites: methotrexate, fluoropyrimidines (e.g. 5-fluorodeoxyuridine (5-FU), and capecitabine), cytarabine, gemcitabine;
(2) Antimitotic agents: taxanes (e.g., docetaxel), vinca alkaloid (e.g. vincristine);
(3) Alkylating agents: carboplatin, cisplatin, oxaliplatin;
(4) Antitumor antibiotics: anthracyclines (e.g. doxil, daunorubicin), podophyllotoxins (e.g. etoposide, teniposide), campothecins (e.g. topotecan, irinotecan);
(5) Tyrosine kinase inhibitors (TKI): imatinib, gefinitib, dasatinib, sunitinib, afatinib, lapatinib, vismodegib;
(6) Cyclin dependent kinase (CDK) inhibitors: alvocidib, palbociclib;
(7) Poly(ADP-ribose) polymerase (PARP) inhibitors: olaparib, rucaparib, veliparib;
(8) Histone deacetylase (HDAC) inhibitors: mocetinostat, belinostat, romidepsin, vorinostat, trichostatin;
(9) Mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitors: selumetinib, trametinib, cobimetinib;
(10) Serine/threonine-protein kinase B-Raf inhibitors: vemurafenib, sorafenib, dabrafenib;
(11) Mammalian target of rapamycin (mTOR) inhibitors: temsirolimus, everolimus;
(12) Phosphoinositide 3-kinase (PI3K) inhibitors: idelalisib;
(13) Ribonucleotide reductase (RNR) inhibitors: cladribine, tezacitabine, fludarabine;
(14) DNA methyltransferase inhibitors: 5-azacytidine (5-AzaC), 5′-deoxy-azacytidine (DAC);

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(15) Retinoids: tretinoin, bexarotene;
(16) Monoclonal antibodies (mAbs): ofatumumab, ibritumomab tiuxetan, rituximab.

These antineoplastic drugs often exert their anticancer effects via several mechanisms of actions and their use in cancer treatment is briefly described below.

2.1 Antimetabolites

Methotrexate, a competitive antagonist of dihydrofolate reductase that participates in the tetrahydrofolate synthesis needed subsequently in thymidine and DNA synthesis, is employed for treating osteosarcomas and trophoblastic neoplasms. 5-FU (Adrucil), an irreversible inhibitor of thymidylate synthase, is indicated for oesophageal, stomach, pancreatic and skin cancers.

2.2 Antimitotic Agents

There are two major classes of antimitotic agents: taxanes and vinca alkaloids, which act as antithesis to each other. Taxanes inhibit tubulin depolymerization in the spindle fiber apparatus, while vinca alkaloids hamper tubulin polymerization.

Docetaxel (Taxotere), a mitotic spindle assembly inhibitor, is FDA-approved for treating locally advanced or metastatic breast cancer, non-small cell lung cancer (NSCLC), head and neck cancer, gastric cancer and hormone-resistant prostate cancer. Vincristine (Oncovin), an inhibitor of mitotic spindle disassembly during metaphase, is widely used to treat acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and neuroblastoma. Vinblastine (Velban), besides preventing the microtubules formation, also hampers glutamic acid metabolism and is approved for several hematological and solid tumors. Vinorelbine (Navelbine), similar in action as vinblastine, is used for treating relapsed metastatic breast cancer.

2.3 Alkylating Agents

Carboplatin (Parapatin), oxaliplatin (Eloxatin) and cisplatin, which crosslink guanine residues, are effective in several forms of cancer. They are able to form inter-strand and intra-strand crosslinks on the guanine residues via the coordination of the N_7 atoms of the purine bases to platinum. The crosslinking ultimately stalls the action of DNA and RNA polymerases. Chlorambucil (Leukeran), a DNA replication interferent, acts against chronic lymphoid leukemia (CLL). All of these agents belong to the WHO's List of Essential Medicines.

2.4 Antitumor Antibiotics

Mitomycin C is FDA-approved for the treatment of adenocarcinomas of the stomach and pancreas, while bleomycin is employed in squamous cell cancer, Hodgkin's disease and germ cell tumors. Doxorubicin (DOX, Adriamycin), a planar anthracycline glycoside antibiotic which intercalates between DNA bases and DNA topoisomerases inhibitor, is a first-line drug for many cancer types, but is primarily used in breast carcinoma, pediatric solid tumors, ovarian cancer and Hodgkin's disease. Etoposide (Etopophos) and teniposide (Vumon) are both DNA topoisomerase II inhibitors for the utilization in leukemia treatment. Irintoecan (Camptosar) and topotecan (Hycamtin) belong to the campothecin family. Both of these DNA topoisomerase I inhibitors are FDA-approved for the treatment of refractory metastatic colon cancer and relapsed ovarian carcinoma, respectively.

2.5 Tyrosine Kinase Inhibitors (TKI)

Gefitinib (Iressa), Afatinib (Gilotrif) and Erlotinib (Tarceva) are widely used to treat NSCLC. Imatinib (Gleevec), another popular TKI that binds to the kinase domain of abelson murine leukemia viral oncogene homolog 1 (abl) in the bcl-abl fusion protein, was approved by FDA in 2001 for treating chronic myeloid leukemia (CML). In 2006, TKI Sunitinib (Sutent) was the first anticancer drug simultaneously approved for two different indications: renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). Vandetanib (Caprelsa) inhibits a rearrangement during transfection (RET)-tyrosine kinase as well as vascular endothelial growth factor receptor (VEGFR), and was FDA-approved for the treatment of late-stage (metastatic) medullary thyroid cancer. Lapatinib (Tykerb), a less commonly known TKI, interrupts the human epidermal growth factor receptor 2 (HER2/neu) and EGFR pathways, and is utilized to treat breast cancer.

2.6 Cyclin Dependent Kinase (CDK) Inhibitors

Alvocidib (Flavopiridol), a flavonoid alkaloid CDK9 kinase inhibitor, interferes with RNA polymerase transcription and halts the cell cycle, which is under clinical development for AML treatment. Palbociclib (Ibrance), a CDK4 and CDK6 inhibitor, is used for treating estrogen receptor (ER)-positive and HER2-negative breast cancer.

2.7 Poly(ADP-Ribose) Polymerase (PARP) Inhibitors

Olaparib (Lynparza) is an FDA-approved targeted therapeutic agents for cancer. Rucaparib and Veliparib are under investigation for use as anticancer agents.

2.8 Histone Deacetyltransferase Inhibitors (HDACi)

Romidepsin (Istodax) was approved in the US for the use against peripheral and cutaneous T-cell lymphoma (PTCL and CTCL). Vorinostat (Zolinza) is FDA-approved for the treatment of CTCL. Mocetinostat, another HDACi, is undergoing clinical trials for treating follicular lymphoma, Hodgkin's lymphoma and AML.

2.9 Mitogen-Activated Protein Kinase (MAPK) Kinase (MEK) Inhibitors

MEK inhibitors hamper the action of the MAPK enzyme (MEK) in the MAPK/extracellular signal-regulated kinase (ERK) pathway. Recently, Cobimetinib (Cotellic), a MEK inhibitor, is FDA-approved to treat advanced melanoma in patients who possess serine/threonine-protein kinase B-Raf proto-oncogene (BRAF) mutations in conjunction with vemurafenib (Zelboraf). Trametinib (Mekinist), a MEK1 and MEK2 inhibitor, was approved in 2013 for metastatic melanoma, while Binimetinib is in phase III clinical trial for neuroblastoma RAS viral oncogene homolog (NRAS)-mutant melanoma.

2.10 Serine/Threonine-Protein Kinase B-Raf Inhibitors

Sorafenib (Nexavar), a FDA-approved drug in 2005 to treat RCC and hepatocellular carcinoma, functions by inhibiting proto-oncogene serine/threonine-protein kinase, platelet-derived growth factor (PDGF) and VEGF. Vemurafenib (Zelboraf) is used for late-stage melanoma.

2.11 Mammalian Target of Rapamycin (MTOR) Inhibitors

Everolimus (Afinitor), an mTOR inhibitor, is FDA-approved for advanced kidney cancer, subependymal giant cell astrocytoma (SEGA), progressive neuroendocrine tumors of pancreatic origin (PNET) and HER2-negative breast cancer in

conjunction with exemestane. Another mTOR inhibitor, Temsirolimus (Torisel), was approved for treating advanced RCC.

2.12 Phosphoinositide 3-Kinase (PI3K) Inhibitors

PI3K inhibitors hinder the PI3K enzymes, which play a significant role in PI3K/protein kinase B (AKT)/mTOR pathway. The first FDA-approved anticancer PI3K inhibitor is Idelalisib (Zydelig) in 2014 to treat various leukemia types. Several other PI3K inhibitors such as Buparlisib and Duvelisib are in Phase III trials.

2.13 Ribonucleotide Reductase (RNR) Inhibitors

RNR inhibitors block the RNR enzyme action by catalyzing deoxyribonucleotides from ribonucleotides. Cladribine and fludarabine (Fludara) are employed for hematological malignancies and hairy cell leukemia (HCL), respectively, while gemcitabine (Gemzar) is used in various carcinomas, NSCLC, pancreatic, bladder, and breast cancer.

2.14 DNA Methyltransferase Inhibitors

Agents such as 5-azacytidine (5-AzaC) and 5′-deoxy-azacytidine (DAC) inhibit the action of DNA methyltransferase that is responsible for DNA methylation.

2.15 Retinoids

There are two different types of retinoid receptors that counteract each other: retinoid X receptor (RXR) and retinoic acid receptor (RAR) that are responsible for the induction of apoptosis and proliferation, respectively. Bexarotene (Targretin) is an FDA-approved RAR activator for CTCL.

2.16 Monoclonal Antibodies (MAbs)

Rituximab (Rituxan), a B cell annihilator, treats mainly lymphoma and leukemia. Trastuzumab (Herceptin), a HER2/neu receptor target, is the first mAb to receive FDA approval and used for breast cancer treatments. Ofatumumab (Arzerra) is

FDA-approved for treating CML that is fludarabine and alemtuzumab (Campath)-resistant. Tositumomab (Bexxar), an immunoglobulin (Ig) G2a anti-CD20 antibody covalently bound to ^{131}I, is also FDA-approved for rituximab-resistant lymphomas expressing CD20. Gemtuzumab ozaogamicin (Mylotarg), an anti-CD33 mAb linked to calicheamicin cytotoxic agent, is FDA-approved for AML in 2000. Panitumumab (Vectibix) targets the extracellular ligand-binding domain of EGFR and is used for patients with non-curable colorectal cancer.

2.17 Combination Therapy

Multidrug resistance (MDR) that results in refractory diseases often necessitates the use of a set of chemotherapy drugs to exert more potent cytotoxic activity against tumor cells (Gottesman 2002; Szakacs et al. 2006). Several factors account for the emergence of MDR, which include increased drug efflux due to the overexpression of both ATP-binding cassette (ABC) transporters and P-glycoprotein (P-GP) (Spencer et al. 2015), alterations in cell cycle checkpoints, overactive EGFR, tyrosine kinase receptor (RTK) and AKT (Gao et al. 2014), expression of multidrug resistance-associated protein (MRP) (Szakacs et al. 2008), and presence of cancer stem cells (Dean et al. 2005). Chemotherapy drugs often act synergistically to render more cytotoxic effect against cancer cells (Mignani et al. 2015). Multidrug regimens are ubiquitously prescribed in clinical practice to combat MDR, and they work via divergent mechanisms. Well-established combination therapies include MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, DOX, and vindesine) for advanced Hodgkin lymphoma, EMA-CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine) for gestational trophoblastic disease (GTD), ADE (cytosine arabinoside, daunorubicin and etoposide) for AML treatment, and G-FLIP (gemcitabine, 5-FU, leucovorin, cisplatin) for pancreatic cancer.

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