Cancer Treatment Drugs

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Summary and Key Points

1. Over eighty different compounds have been approved to treat cancer. Their mechanisms of action, effectiveness against specific cancers, and potential toxicity vary greatly.
2. Cytotoxic chemotherapy agents kill by damaging essential cellular components. It is useful to consider these compounds by their mechanism of action:
    a. Alkylators damage DNA by adding a carbon adduct covalently to specific bases.
    b. Platinum analogues, like alkylators, covalently add platinum to DNA.
    c. Topoisomerase inhibitors damage DNA by interfering with the action of an enzyme needed for unwinding DNA for replication and transcription.
    d. Microtubule inhibitors disrupt mitosis by damaging the structure needed for the physical separation of chromosomes into daughter cells.
    e. Antimetabolites interfere with DNA synthesis by depleting pools of nucleotides.
3. “Targeted Therapies” refer to agents that interact with a specific cell target to kill or inhibit cell growth.
    a. Hormonal agents interfere with hormones that stimulate cancer growth.
    b. Kinase inhibitors interfere with specific growth factor receptors or intracellular messengers that have a tyrosine kinase function.
    c. Antibodies bind specifically to protein targets on the surface of cancer cells.
4. Immune therapy of cancer has only recently become a widely applied modality of care.
    a. Checkpoint inhibitors disrupt regulatory components of the immune response to permit immune-mediated destruction of tumors.
    b. Cytokines such as interferon and interleukin-2 are now rarely used to treat cancer.
    c. Despite much hope, no vaccine has ever effectively treated cancer.

Introduction

What we now call cancer, the uncontrolled and ultimately lethal over-growth of tumor cells, has been recognized for many centuries. However, the systematic development of drugs to kill cancer cells dates back only 70 years when biologic warfare studies demonstrated the ability of mustard compounds to destroy lymphocytes and bone marrow cells, and ultimately, lymphoma cells. The first class of anti-tumor drugs is now known as the alkylating agents. Over the following 50 years, many other classes of drugs came into clinical use, collectively known as cytotoxic drugs, directly damaging DNA, interfering with the synthesis and replication of DNA, and impairing function of the mitotic spindle.

During the late 1990’s, the quest for new cancer cell toxins gave way to the development of “targeted” agents, mainly in the form of monoclonal anti-bodies and small molecule kinase inhibitors that interfere with receptor function and signaling cascades. The hope is that biologic processes unique to cancer cells can be drug targets and that normal cells can be spared “off target” effects, thus avoiding many of the toxicities associated with chemotherapy.

This chapter will describe, in terms of mechanism of action, the most important classes of cytotoxic and targeted therapies as well as their

most characteristic side effects and clinical uses. Table 1, summarizing the classes of drugs and representative members of those classes, is included at the end of the chapter. Rather than an encyclopedia, this will be a schematic diagram or roadmap to more detailed knowledge that you will acquire during your clinical training and subsequent experience. The modern pharmacology texts such as Katzung[1], Golan[2], and others will build on this framework.

The Cytotoxics

Alkylating agents were the first modern anti-cancer drugs. The nitrogen mustards, initially used to kill soldiers during the trench warfare of World War I, were later shown to be particularly destructive to lymphocytes and to bone marrow cells. Early clinical trials demonstrated their ability to shrink lymphoma tumor masses. The unifying mechanism of action is transformation of a pro-drug to an active compound from which an alkyl group is detached, which binds covalently to nucleophilic groups such as N1 and N3 adenine, resulting in interstrand cross-linking of the DNA double helix. This results in base pair mismatches, base excisions and DNA strand breakage, which then trigger the process of "programmed" cell death, known as apoptosis.

The prototype alkylating agent is cyclophosphamide, activated in the liver via P 450 enzymes. The drug is most often used to treat breast cancer and the non-Hodgkin lymphomas. Side effects include suppression of the red and white blood cells and platelets (myelosuppression), nausea and vomiting, hair loss, ovarian/testicular failure and late occurrence of leukemia.

Similar in mechanism of action to the classic alkylators are the platinum drugs, which covalently bind platinum to bases in the same DNA strand instead of across strands, like classic alkylators. The result of intrastrand covalent cross-linking is the same-direct DNA damage that triggers apoptosis.

Three different platinum drugs- Cisplatin, Carboplatin, and Oxaliplatin are clinically important and share the same mechanism of action. Each platinum compound has distinctive clinical uses and toxicity profiles:

- They all depend on renal excretion and have the potential to damage the kidney, though cisplatin has the greatest potential for nephrotoxicity.
- They have a broad spectrum of anti-tumor activity and are among our most useful cytotoxic drugs.
- They produce bone marrow suppression to varying degrees.

Cisplatin and Oxaliplatin cause peripheral sensory neuropathy.

The third class of cytotoxics to be discussed, the antimetabolites, was historically the next class developed after the alkylators, beginning with the work of Dr Sydney Farber in Boston in the late 1940's. The generic definition of an antimetabolite is a compound that mimics the structure of purines and pyrimidines- the building blocks of DNA/RNA - and/or inhibits the enzymes that synthesize these building blocks and incorporate them into DNA/RNA.

The earliest example of an antimetabolite, methotrexate, inhibits the enzyme, dihydrofolate reductase (DHFR), critical for methyl group transfers in purine synthesis. It is important to note that the antibiotic trimethoprim (frequently combined with a sulfa antibiotic in clinical use) inhibits bacterial DNA DHFR by the same mechanism.

The most commonly used antimetabolites today are fluorouracil and its oral prodrug capecitabine. Both of these drugs impact DNA synthesis by inhibiting the enzyme thymidylate synthase, essential in pyrimidine synthesis/incorporation into DNA.

Fluorouracil and capecitabine are most important in the treatment of gastrointestinal cancers, particularly colon cancer. Capecitabine is also used in the treatment of breast cancer. Diarrhea, mouth sores and bone marrow suppression are their most important side effects.

We have so far discussed drugs which directly damage DNA-the alkylators and platinums, which interfere with purines and pyrimidine synthesis and incorporation into DNA/RNA –the antimetabolites. We move now to an important class of drugs which interfere with function of the enzyme family called topoisomerases. These enzymes break, uncoil and religate DNA strands during the complex process of replicating the double helix. Without topoisomerase's function, DNA replication cannot occur.

The most important group of topoisomerase inhibitors is the anthracyclines, which inhibit topoisomerase II, resulting in DNA strand breaks, thereby triggering apoptosis. In addition, these drugs generate free radicals which may be particularly important in causing damage to

heart muscle. This menacing toxicity limits the amount of anthracycline that can be given. Cumulative doses above a well-defined threshold produce a rapidly escalating probability of heart failure, which pathologically is due to myocardial necrosis.

Doxorubicin (almost always called by its original proprietary name Adriamycin) is the prototype anthracycline. It has potent anti tumor activity against multiple tumor types, including breast cancer, lymphomas, acute leukemia and soft tissue sarcomas. In addition to heart damage, doxorubicin and related drugs cause severe hair loss, bone marrow suppression, tissue necrosis when extravasated during IV administration, and vomiting-especially when combined with other drugs e.g. cyclophosphamide.

The inhibitors of topoisonmerase I also interfere with the critical processes of breakage, uncoiling and relegation of DNA strands during replication. The prototype drug irinotecan is important in the treatment of gastrointestinal cancers. Its main toxicities are hair loss, bone marrow suppression and diarrhea. It does not cause cardiac toxicity.

The final classes of cytotoxic drugs we will consider damage the mitotic spindle, which guides duplicated chromosomes to daughter cells. The mitotic spindle is built of assemblies of microtubules, which act as "tracks" for the chromosomes. They are in a constant state of assembly and disassembly.

Well in advance of detailed knowledge of microtubule biology, the vinca alkaloids, derived from the periwinkle plant, were developed over forty years ago. They bind to β-tubulin, one of the proteins making up microtubules, and prevent tubulin / microtubule polymer assembly.

The prototype vinca alkaloid, vincristine, is now used almost exclusively in the treatment of lymphoma. The most important vinca in current oncological practice is vinorelbine, which is particularly useful in treating breast cancer and lung cancer. Like the platinum compounds, the vinca alkaloids have different side effect profiles. The parent compound, vincristine, is not myelosuppressive but causes substantial neurotoxicity. Vinorelbine causes much less neurotoxicity, and bone marrow suppression limits its dosing. The vinca alkaloids cause little hair loss and little nausea/vomiting.

The second group of "spindle poisons" is also plant derived, from the yew tree, and are the taxanes. Two important drugs, paclitaxel and docetaxel, prevent disassembly of the microtubules, i.e. they "hyperstabilize" and in so doing disrupt the function of microtubules. Both of these drugs are useful in a broad range of tumor types, including breast cancer, lung cancer, head and neck cancer and ovarian cancer. Like the vinca alkaloids they produce peripheral neuropathy. They also cause hair loss and myelosuppression. Because of their formulation, which has to include a detergent to get them into aqueous solution, they frequently cause allergic reactions.

Targeted Therapies

Targeted therapy implies drug treatment directed at a particular tumor cell biologic characteristic such as expression of the estrogen receptor or over-expression of the HER2 gene. In the first example, many breast cancers will shrink when estrogen, the ligand of the receptor, is withheld. In the second example, binding of the HER2 receptor with a monoclonal antibody, or inhibition of the tyrosine kinase activity of the receptor (which triggers a signaling pathway), will cause shrinkage of most HER2 breast cancers.

An early approach to "targeted" therapy occurred in 1896, when an English surgeon, Beatson, carried out oophorectomy in an attempt to treat advanced breast cancer. His understanding of sex steroid physiology was embryonic, but the concept of removing a female reproductive organ to treat a cancer occurring almost exclusively in women was the beginning of what we call hormonal or endocrine therapy. Armed with the knowledge that estrogen stimulates proliferation of breast cancer cells that express the estrogen receptor and that testosterone, in similar fashion, stimulates proliferation of prostate cancer cells, most of which express the androgen receptor, multiple strategies to deprive these tumors of their growth factors have been devised.

In 1941, Huggins and his colleagues demonstrated that castration of rodents with prostate cancer resulted in regression of prostate cancer. Androgen deprivation remains the cornerstone of treating metastatic prostate cancer today, and is now accomplished pharmacologically instead of by surgical castration.

The pituitary gland, which secretes Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) does so in response to pulsatile signaling from the hypothalamus with luteinizing hormone releasing hormone (LHRH). When the signal becomes monophasic, for example after a

large parenteral dose of an LHRH analog such as goserelin or leuprolide, the pituitary cannot respond and gonadotropin signaling stops with the consequence that testosterone production in the testicles ceases. In like fashion, LHRH analogs suppress of ovarian estrogen production.

Seventy per cent of men with prostate cancer experience tumor regression with testosterone deprivation, and 50-60% of women with estrogen receptor positive (ER+) breast cancer experience tumor regression with estrogen deprivation.

Ovarian suppression in breast cancer is most effective in pre menopausal women, whose ovaries are producing large quantities of estrogen. Another strategy for estrogen deprivation is to block the estrogen receptor with tamoxifen, a drug developed in Worcester during the late 1960's.[3] Tamoxifen is a competitive inhibitor of estrogen binding to the estrogen receptor. It has both estrogen agonist and antagonist properties and is frequently referred to as a selective estrogen receptor modulator (SERM). Hence, it typically acts as an estrogen antagonist in breast tissue, making it useful in treating advanced breast cancer, in reducing recurrence late in early stage breast cancer and in preventing breast cancer in many women at high risk. Tamoxifen's estrogen antagonist property is also responsible for the most common side effect of the drug, hot flashes. The estrogen agonist function of tamoxifen produces the beneficial result of reducing the risk of osteoporosis and fracture. However, estrogen activity of tamoxifen is the cause of increased risks of uterine cancer and deep vein thrombosis associated with the drug.

An alternative strategy of estrogen deprivation, effective only in postmenopausal women with ER+ disease, is to inhibit or inactivate the enzyme aromatase, which catalyzes the transformation of steroid precursors into estrogens. The so called aromatase inhibitors, with anastrozole the prototype compound, have essentially the same therapeutic indications as tamoxifen-with the main difference being that anastrozole and its cousins letrozole and exemestrane work only in post menopausal women. Side effect profiles are also different. Because they produce near total elimination of circulating estrogens, the aromatase inhibitors accelerate bone loss and can cause joint discomfort. However, they do not increase the risks of uterine cancer or thrombosis.

A final agent causing estrogen deprivation to treat breast cancer is the drug fulvestrant, given as a monthly intra muscular injection. This drug accelerates degradation of the estrogen receptor and down regulates its production. Since it has no agonist activity it has been called a pure anti-estrogen. Currently it is used only to treat advanced disease. Its major toxicity is menopausal symptoms.

The study of breast cancer biology has yielded other important targets for drug treatment, particularly the HER2 (also called erb2 or neu) cell surface receptor and its intracellular kinase which activates signaling cascades concerned with proliferation and cell maintenance. A monoclonal antibody binding to the extracellular domain of HER2, Trastuzumab (commonly known as Herceptin) has revolutionized the treatment of HER2 over-expressing breast cancers of every stage. In addition, the small molecule, lapatinib, which blocks phosphorylation of the intracellular tyrosine kinase activity of HER2, has also come into clinical use in breast cancer.

The model for monoclonal antibody directed against a surface receptor target is also clinically exploited in the treatment of non Hodgkin lymphoproliferative disorders with the anti-CD20 antibody, rituximab, and the treatment of colorectal cancer with the EGFR monoclonal antibody cetuximab.

In general, because monoclonal antibodies have high specificity for their binding sites, these drugs produce mild toxicities related mainly to infusion reactions (they are all given IV). However trastuzumab can cause (usually mild) cardiac toxicity, rituximab can cause leucopenia and immunosuppression and cetuximab can cause rash and diarrhea. Monoclonal antibodies used in cancer treatment are "humanized" and typically have very long half-lives. This permits them to be given relatively infrequently (weekly to every other month) and yet still maintain circulating blood levels of the drugs throughout treatment.

In this century kinase inhibitors have become a common class of "targeted" oral anti-cancer drugs. Preventing phosphorylation by intracellular kinases which drive proliferation has been exploited most elegantly and effectively with the development of imatinib, the small molecule tyrosine kinase inhibitor which emerged as a "miracle drug" in the treatment of chronic myelocytic leukemia. Imatinib and its descendants interrupt the constitutive activation of the bcr-abl protein in CML, shutting down the hyper proliferation of myeloid cells and delaying/preventing the previously inevitable progression to a fatal acute leukemia-like blast crisis. Interruption of the bcr-abl activity results in

suppression of the malignant CML clone(s) as evidenced by normalization of cytogenetics and in many patients, suppression of the bcr-abl protein product.

In keeping with the hopes for targeted therapy, imatinib toxicity is minimal and only rarely necessitates stopping treatment. However, imatinib also demonstrates that so-called “targeted” kinase inhibitors can have multiple targets. The stem cell factor receptor and platelet derived growth factor receptor are both inhibited be imatinib. While inhibition of these other targets has been exploited by using imatinib to treat other malignancies (gastrointestinal stromal tumor and hypereosinophilia syndrome), additional targets may also mediate some of the side effects of the drug. Subsequent kinase inhibitors have often had even more side effects than imatinib, generally because many of them can interfere with multiple kinases.

At this point there are over twenty kinase inhibitors available to treat various cancers. All are oral drugs. Like imatinib, some are only used if a cancer expresses a particular target inhibited by the drug. For example, erlotinib inhibits the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) and is used to treat lung cancers that harbor activating mutations in EGFR. However, many kinase inhibitors are used to treat an array of cancers regardless of the presence of a specific mutation. Examples are sunitinib, useful in renal cell cancer and sorafenib, one of the first drugs to be effective to any degree in treating primary liver cancer. These compounds are really “multi-targeted” kinases and interfere with a number of intracellular proteins. They tend to cause many more side effects than seen with more specific kinase inhibitors, like imatinib.

Some targeted therapies have been designed based on the concept of anti-angiogenesis, or blocking tumor blood vessel formation. The concept, originally articulated and demonstrated in the laboratory by the late Judah Folkman at Children’s Hospital Boston, proposes that tumor growth can be halted by preventing the development of the new blood vessels needed to nourish/oxygenate tumor masses. The drugs which have anti-angiogenic activity are drawn from several classes. The monoclonal antibody, bevacizumab, binds to the vascular endothelial growth factor receptor called, VEGF. The tyrosine kinase inhibitors sunitinib and sorafenib, discussed above, inhibit intra-cellular signaling pathways that drive angiogenesis. The immunomodulatory agents, thalidomide and lenalidomide, inhibit new blood vessel formation by uncertain mechanism. Much remains to be learned regarding the precise mechanisms by which these varied agents inhibit tumor blood vessel development.

Immune Therapy

Using the immune system to treat cancer has been a goal of medicine for at least the last century. There have been many attempts to develop vaccines, cytokines, and antibodies to treat cancer immunologically. Despite much hope and promise, no cancer vaccine has been effective. Cytokines such as interferon and interleukin-2 do have activity against some cancers and are approved by the FDA, but their activity is limited and they have significant toxicity. Only in the last few years has there been a real breakthrough in immune therapy of cancer.

The human body clearly can generate an immune response to cancers. A biopsy of a cancer will frequently show a large number of tumor-infiltrating lymphocytes (TIL) within the tumor. Some studies have correlated the presence of TIL with better outcomes in some cancers (melanoma, breast). However, despite the presence of an immune response, most cancers evade immune surveillance. One mechanism by which this is accomplished is using checkpoints on regulatory T cells to shut down the immune response. In the last few years a number of antibodies have been developed that inhibit these checkpoints.

Ipilumumab binds CTLA-4, and pembrolizumab and nivolumab bind to PD-1. All of these drugs are antibodies and their respective targets are protein receptors on regulatory T cells that are used to down-regulate the immune response. Antibody binding to these receptors inhibits their function and prevents shut down of the immune response. Ipilumumab is approved for treatment of melanoma and pembrolizumab and nivolumab are approved for treatment of melanoma, non-small cell lung cancer, and renal cell cancer. These drugs can cause prolonged remissions of cancer. The major side effects of the drugs are, not surprisingly, auto-immune toxicities. Autoimmune colitis, pneumonitis, and endocrinopathies have been the most commonly observed side effects. Toxicity seems to be greater with ipilumumab than the other antibodies, possibly because CTLA-4 is expressed earlier in regulatory T cell development than PD-1, and so inhibition of CTLA-4 may result in broader immune regulatory suppression. Additional checkpoint inhibitors are in development, and it is likely that additional cancers will be treated with these drugs in the future.

Conclusion

Space and the immense volume of information demanding your attention have precluded a comprehensive review of all the important drugs and a more detailed description of mechanisms of action, clinical uses and toxicities. As noted in the introduction, this diagram or roadmap, will serve as a skeleton which will be “fleshed out” as your clinical training and experience unfold.

The biology of cancer is complex and dynamic with tumor biology evolving during the course of an individual patient’s illness and treatment. Biology of cancer cells and normal cells overlaps extensively, what we describe as clinical cancer represents the behavior of multiple clones or families of tumor cells which are heterogeneous because of an increased DNA mutation rate, resulting in a daunting challenge for anti cancer drug treatment.

Table 1. Classes of Drugs Reviewed in this Chapter

1. Cytotoxic Agents
   a. Alkylators
      Nitrogen Mustard, Cyclophosphamide
   b. Platinum Compounds
      Cisplatin, Carboplatin, Oxaliplatin
   c. Antimetabolites
      Methotrexate, Fluorouracil, Capecitabine
   d. Topoisomerase Inhibitors
      Doxorubicin, Irinotecan
   e. Microtubule Binding Agents
      Vincristine, Vinorelbine, Paclitaxel, Docetaxel
2. Targeted Therapies
   a. Hormonal Therapies
      Leuprolide, Goserelin, Tamoxifen, Anastrozole, Letrozole, Exemestane, Fulvestrant
   b. Antibodies
      Trastuzumab, Rituximab, Bevacizumab, Cetuximab
   c. Tyrosine Kinase Inhibitors
      Imatinib, Sunitinib, Sorafenib, Erlotinib, Lapatinib
   d. Immune Modulators
      Thalidomide, Lenalidomide
3. Immune Therapy
   a. Checkpoint Inhibitors
      Ipilumumab, Pembrolizumab, Nivolumab

Thought Questions

1. Anti-cancer drugs are frequently used in combinations. The goal of combination chemotherapy is to increase tumor cell kill without causing unacceptable toxicity. What drugs might be difficult to combine together? For example, what might be the consequence of concurrent treatment with doxorubicin and trastuzumab? What toxicity might limit the combination of vincristine and paclitaxel?

   Your answer:

Expert Answer

2. One uncommon but very serious late side effect of alkylating agents and topoisomerase inhibitors is the development of myelodysplasia or acute myeloid leukemia. How might these drugs cause hematologic malignancies?

   Your answer:

Expert Answer

3. The monoclonal antibodies cetuximab and panitumomab both target the extracellular domain of EGFR and are effective in the treatment of colon cancer. However, colon cancers that have mutations in KRAS are completely resistant to treatment with these antibodies. What could be the mechanism of resistance of cells with KRAS mutations to EGFR inhibition?

   Your answer:

   Expert Answer

4. A very common mechanism of resistance to many chemotherapy drugs is the expression of a cell surface protein on cancer cells called *mdr* (for multi-drug resistance; it has also been called P170). *Mdr* is an ATP-dependent "pump" that transports molecules out of the cell. Planar, lipophilic molecules tend to be good substrates for *mdr*. Interestingly, many chemotherapy drugs derived from natural sources are transported out of cancer cells by *mdr*. Which chemotherapy drugs are likely to be substrates for *mdr*?

   Your answer:

   Expert Answer

Glossary

Mechanism of action- How a drug interacts with a target

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