Principles of Medical Oncology

James Liebmann, MD
Richard S. Pieters, MD

Citation: Liebmann J, Pieters RS. Principles of Medical Oncology. In: Pieters RS, Liebmann J, eds. *Cancer Concepts: A Guidebook for the Non-Oncologist.* Worcester, MA: University of Massachusetts Medical School; 2016. doi: 10.7191/cancer_concepts.1020.

This project has been funded in whole or in part with federal funds from the National Library of Medicine, National Institutes of Health, under Contract No. HHSN276201100010C with the University of Massachusetts, Worcester.

Summary and Key Points

1. Medical oncologists are internists specializing in the care of the adult cancer patient. They frequently function as a primary care physician for patients with cancer. Pediatric hematology/oncology is a separate subspecialty, covered in a separate chapter, Pediatric Oncology Principles.
2. Medical oncologists often direct the evaluation of patients with newly diagnosed cancers, maintain ongoing follow-up of cancer patients after initial treatment has ended, and often supervise hospice care for cancer patients at the end of life.
3. Medical oncologists prescribe chemotherapy to treat cancer.
4. Chemotherapy refers to drug therapy and usually is used to treat the whole body, although few drugs effectively penetrate the brain.
5. “Chemotherapy” refers to over 100 different drugs that are used to treat cancers. Each drug has a unique mechanism of action and unique side effects.
6. Only a small number of cancers are able to be cured when treated solely with chemotherapy.
7. Chemotherapy can improve cure rates of cancers when given in conjunction with surgery and/or radiation.
8. Chemotherapy can prolong survival in patients with incurable cancers and can also relieve symptoms caused by cancers.
9. Patients receiving chemotherapy must be assessed frequently to prevent intolerable side effects and ensure the chemotherapy is working against the cancer that is being treated.

Introduction

Medical oncology is the branch of Internal Medicine that specializes in the treatment of cancer in adult patients. Most medical oncologists are also hematologists, who specialize in the treatment of hematologic malignancies (the leukemias, lymphomas and myelodysplastic syndromes) as well as benign blood disorders and blood treatments. Because the most common pediatric malignancy is leukemia, pediatric oncologists are always hematologist/oncologists. Since medical oncologists are internists or pediatricians, they manage the complex medical conditions which frequently occur in cancer patients. Medical oncologists also prescribe chemotherapy.

Medical oncology developed after the introduction of modern drug treatment for cancer, which began after World War II. Informal training was available by the early 1960s, but medical oncology was only recognized as a new subspecialty of Internal Medicine in 1972[1] and pediatrics in 1974.[2]

Modern drug treatment of cancer dates to World War II when Gilman and colleagues launched the first clinical trials of nitrogen mustard. Since then, over one hundred different drugs have been approved in the United States for the treatment of cancer. While the general public– and many physicians– commonly lump all these drugs under the name “chemotherapy”, there is tremendous variation in the mode of action and toxicity of these different compounds. Anti-cancer drugs can work by mobilizing the immune system (e.g., interleukin-2, ipilumumab), blocking hormones (e.g., tamoxifen), interrupting intracellular pathways (e.g., temsirolimus), or mutating DNA (e.g., nitrogen mustard) to list a few mechanisms of their actions. Similarly, side effects from antineoplastics can range from life-threatening bone marrow suppression to emotionally distressing alopecia. Despite the fact that these drugs may all be labeled “chemotherapy”, it should be appreciated that there are different indications, mechanisms, and toxicities for each agent.

This chapter will review the practice of medical oncology and some general principles followed in the use of chemotherapy. Concepts including goals of chemotherapy treatment, evaluation of the effects of chemotherapy, integration of chemotherapy with other cancer treatments, and use of combinations of chemotherapy drugs will be covered. Those interested in specific aspects of the drugs are referred to the section on chemotherapy of neoplastic diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics.

The Practice of Medical Oncology

Medical Oncologists are internists with three years of residency in Internal Medicine before they start training in Oncology. As a result, they are prepared to manage all of the complex medical issues that arise during the course of treatment, whether caused by the treatment or by underlying conditions, with the same consultative support from other specialists that primary care physicians would require.

Included among the many conditions managed by medical oncologists are febrile neutropenia, sepsis, anemia, thrombocytosis, thrombocytopenia, deep venous thrombosis, seizures, elevated blood sugar, peripheral neuropathy dehydration tumor lysis syndrome, and metabolic derangements, all of which can be caused by chemotherapy, and some of which may be caused by cancer. They must be prepared to manage severe pain. They often have to refer to another specialist for help with tumor bleeding or a pathologic fracture.

In addition, Medical Oncologists must understand the randomized trial data justifying the use of each chemotherapy regimen, the risks and benefits of each drug and drug combination, and the interaction of each regimen with patient's comorbid conditions, such as diabetes, renal failure or heart disease. Specialized oncologists prescribe and supervise bone marrow transplantation, a set of treatments which requires intensive care level skills.

In the United States, medical oncologists are the physicians who admit most cancer patients to the hospital, except for patients who require a surgical intervention. A good Medical Oncologist views his/her practice as providing a medical home for the oncology patient during and shortly after the course of treatment. They are the physicians most likely to provide supervision for hospice care for their patients

Goals of Chemotherapy Treatment

When faced with a problem, it is natural to want to find a solution. Meeting a patient with a malignancy, it is understandable that a physician's first hope is to find a cure for the patient's cancer. Unfortunately, many human cancers are simply not curable at present. Before initiating any anti-cancer treatment, it is important to ask what the goal of treatment is. If cure is possible, then that should be the goal of treatment and both patient and physician may be willing to accept side effects of treatment in exchange for cure. If cure is not possible, then goals may be more modest, such as prolongation of life or relief of symptoms. In such circumstances, choices of treatment may be greatly affected by considerations of complications of treatment. This section will consider the use of chemotherapy in anti-cancer treatment based on treatment goals.

Treatment for Cure

Table 1 lists the cancers that are curable, even at an advanced stage, with chemotherapy alone. For the most part, the curative regimens for these diseases involve multiple chemotherapy agents given at well-established doses and schedules. Many of these regimens have evolved over decades of clinical trials (e.g., treatment of childhood acute lymphoblastic leukemia) while others have not changed in a quarter-century (e.g., treatment of germ cell tumors). Over the past fifty years, a fundamental principle of curative chemotherapy regimens has been that a complete response to treatment is necessary to achieve a cure. A complete response is defined as the eradication of all known tumor as assessed by physical exam, imaging studies such as CT or other scans, and, when indicated, biopsy of involved areas such as bone marrow. Unfortunately, while cure is impossible in the absence of a complete response, relapse of undetected microscopic cancer can and does happen in patients who appear to have achieved a complete response.

Table 1. Cancers Potentially Curable by Chemotherapy Alone
Pediatric Cancers
Acute Leukemia
Hodgkin and Non-Hodgkin Lymphoma
Wilms Tumor
Embryonal Rhabdomyosarcoma
Adult Cancers
Acute Leukemia
Hodgkin and Non-Hodgkin Lymphoma
Germ Cell Cancers
Choriocarcinoma

All of the treatments for the diseases listed in Table 1 are given for a defined period of time, after which treatment is stopped and patients are then either cured or fated to relapse at some point in the future. New drugs have challenged the idea that intensive, limited treatment with complete eradication of all tumor cells is the only way to control cancer. These drugs also force us to revise our understanding of what constitutes "cure". Imatinib is highly active against chronic myeloid leukemia (CML) with complete response rates of over 90% and 5-year disease free rates of 85-90%. However, it appears that it is necessary for patients to stay on imatinib for a long time, possibly life-long, as relapse of CML has occurred in patients who stop the drug even after years of use. In a sense, one can think of current treatment of the cancers listed in Table 1 as analogous to treatment of many bacterial infections where patients are cured after short courses of antibiotics. By contrast, treatment of CML with imatinib can be likened to treatment of other chronic diseases (hypertension, diabetes, HIV) where continuous treatment controls disease and permits long term survival.

While the list of diseases cured solely by chemotherapy is short, there are many cancers in which the use of chemotherapy in combination with surgery and/or radiation will markedly increase cure rates. In most of these settings chemotherapy is considered an "adjuvant" (or aide) to the "primary" treatment of surgery or radiation. "Neoadjuvant" chemotherapy refers to giving chemotherapy before the patient undergoes surgery or radiation, while "adjuvant" chemotherapy is given after primary surgery or radiation. In either setting, the use of chemotherapy in addition to surgery or radiation is believed to improve survival by eradicating microscopic metastatic disease not cured or removed by the local treatment. Table 2 lists diseases for which adjuvant or neoadjuvant chemotherapy is commonly employed. In each case, the diseases are early-stage, that is, not widely metastatic.

Table 2. Adult Cancers in which Chemotherapy Increases Cure Rates
Stage I-III Breast Cancer
Stage II- IIIa Non-Small Cell Lung Cancer
Limited Stage Small Cell Lung Cancer
Embryonal Rhabdomyosarcoma
Stage III Colon Cancer
Stage II-IV Head and Neck Cancers

Table 3. Pediatric Cancers Treated with Adjuvant Chemotherapy
Limited stage Wilms tumor
Neuroblastoma
Rhabdomyosarcoma

Table 4. Pediatric Cancers that could (and have been) Treated with Chemotherapy as Primary Treatment
Resected high grade brain tumors
Non-metastatic Ewing sarcoma
Non-metastatic osteosarcoma
Stage I-III malignant germ cell tumors

The use of chemotherapy in the neoadjuvant or adjuvant setting results in a different distribution of patient outcomes than occurs with the use of curative chemotherapy for diseases listed in Table 1. For example, patients with Stage IV diffuse large cell non-Hodgkin lymphoma will all die without treatment but have a 40-50% probability of cure with current standard chemotherapy. By contrast, a 60 year old woman with a 2.5 cm estrogen-receptor positive, lymph node negative breast cancer has about a 60% chance of being relapse-free ten years after mastectomy or lumpectomy and breast irradiation without any additional chemotherapy.

If that patient receives an anti-estrogen therapy like an aromatase inhibitor for five years after her surgery, her probability of relapse-free survival at ten years improves to 77%. If she takes chemotherapy in addition to her aromatase inhibitor after surgery, her probability of relapse-free survival at ten years is now 84%.[3] In the case of patients with Stage IV non-Hodgkin lymphoma, chemotherapy is the only treatment modality that results in a meaningful chance of cure. However, surgery will cure the majority of women with early stage breast cancer and the use of chemotherapy in such patients, while improving overall survival, results in over-treatment of those who were cured by their surgery. A major goal of clinical research is to better define patients who will benefit from adjuvant or neoadjuvant chemotherapy to avoid exposing those patients who do not require chemotherapy to potential side effects of over-treatment.

Neoadjuvant chemotherapy is most often employed in situations for which surgery may result in a significant functional or cosmetic defect (e.g., laryngeal or anal cancer or breast cancer). In these settings, eradication of the primary tumor by chemotherapy – given with radiation in some diseases – can eliminate the need for or lessen the extent of subsequent surgery. Neoadjuvant chemotherapy can also be given in settings in which it is better tolerated than post-operative chemotherapy (e.g., rectal cancer).

Treatment for Palliation of Symptoms or Prolongation of Life

In the large number of advanced cancers for which cure is not possible, the major goals of any treatment, including chemotherapy, are to relieve symptoms of the cancer and prolong life. There is now good evidence that current chemotherapy can result in significant prolongation of life in a number of common tumors, including metastatic lung, breast, and colorectal cancers. Quality of life studies are increasingly incorporated into clinical trials of chemotherapy in advanced malignancies, making it possible to identify drugs which can reduce symptoms of cancer even if they have no or minimal impact on the duration of survival.

Given that a major goal of treatment of advanced cancers is the relief of symptoms; it becomes a Pyrrhic victory if metastatic tumors are shrunk at the expense of diminished quality of life from excessive chemotherapy toxicity. Careful monitoring of patients throughout treatment is essential. Many side effects of chemotherapy can be managed with simple, inexpensive treatments such as anti-emetics for nausea, mouth washes for stomatitis, or creams for rashes. Other toxicities will require reductions in chemotherapy doses or delays in treatment for symptoms to resolve. Note that this approach is in contrast to the treatment of curable malignancies where dose delays or reductions can compromise the chance of cure or long term survival. In addition to careful monitoring of patients, constant communication with patients throughout treatment is also vital. Some patients with advanced tumors may accept an increased risk of side effects from treatment if their major goal is prolongation of life; others may wish to spend as little time as possible in the clinic or hospital receiving treatment or prefer to forgo a chance at a somewhat longer life in favor of fewer complications of treatment.

Evaluating Effects of Chemotherapy

A fundamental principle of pharmacology is the therapeutic index. Easily defined, but somewhat difficult to calculate with precision, it is the benefit of a drug divided by the drug's toxicity. Given the potential side effects of chemotherapy, it is easy to appreciate that the therapeutic index of chemotherapy can be small. Because of this, it is vital that patients undergoing chemotherapy treatment be continually re-assessed for the benefits and side effects of treatment.

The most common assessment of benefit from chemotherapy is measurement of tumor response to treatment. This can be done via physical exam of palpable tumors, measurement of tumors found on radiographic studies, measurement of serum tumor markers, or repeated biopsies of areas of known tumor. A "partial response" to treatment is usually defined as a reduction by 50% or more of all known measurable tumors with no evidence of new tumor growth. As mentioned previously, a "complete response" is the eradication of all known tumor. "Progressive disease" has been defined as the appearance of new tumors or growth by 25% of existing tumors and "stable disease" is a cancer that has neither demonstrated a partial response nor progressed. The importance of these designations lies in the clinician's use of them. It makes no sense, for example, to continue ineffective chemotherapy in a patient who has progressive disease on treatment. By contrast, it may be worthwhile to continue treatment in a patient who has developed a partial response or stable disease if their quality of life is acceptable on treatment. Finally, as previously noted, assessment of complete response is important in treating potentially curable tumors.

Assessment of side effects of treatment is as important as assessment of tumor response. Formal definitions and grading of side effects have been published[4] and are routinely utilized in assessing treatments in clinical trials. Patients should be seen frequently while receiving chemotherapy and steps should be taken to prevent or alleviate side effects as soon as possible. Particularly in the patient with an incurable malignancy, it is imperative that the goals of treatment be continually evaluated in light of side effects of treatment.

Integration of Chemotherapy with Other Anti-Cancer Treatments

A common theme of this book is that many patients with cancer will require more than one kind of treatment. A patient with early stage breast cancer may undergo a lumpectomy, then receive post-operative (adjuvant) chemotherapy, receive radiation to the residual breast after chemotherapy is complete, and then conclude treatment by taking tamoxifen or an aromatase inhibitor for five to ten years. A patient with rectal cancer could start treatment with chemotherapy given concurrently with radiation, followed by surgery to remove residual tumor, and conclude treatment with additional chemotherapy. Another patient with limited stage small cell lung cancer will likely be treated with thoracic radiation given concurrently with chemotherapy, followed by additional chemotherapy, and then receive prophylactic cranial irradiation (PCI). Each of these cases demonstrate the variety of options facing patients and physicians treating cancer and highlights the need for good communication between medical, surgical, and radiation oncologists to coordinate care successfully.

Concurrent chemotherapy and radiation have been shown to be superior to sequential treatments in a number of cancers. Theoretically, chemotherapy could treat microscopic metastatic disease that exists outside the radiation treatment field and so improve cure rates by preventing relapse of disease not treated by radiation. Additionally, a number of chemotherapy drugs can increase the radiation sensitivity of tumor cells. This property of radiation sensitization should lead to fewer relapses of tumors within the radiation field, compared to similar tumors treated with radiation alone. In fact, most successful trials of concurrent radiation and chemotherapy treatment have demonstrated a reduction in both local and distant cancer relapses with concurrent treatment as compared with sequential treatment or radiation treatment alone. However, concurrent treatment also comes with a higher cost of increased toxicity. In addition to the unique side effects that may be associated with any chemotherapy drug, chemotherapy given concurrently with radiation can increase the risk and severity of both acute and late side effects associated with radiation.

Use of Combinations of Chemotherapy Drugs

While individual chemotherapy drugs can have significant activity against tumors as assessed by tumor response rate, most regimens that are used to cure cancers (Tables 1 and 2) include multiple chemotherapeutic agents. Using drugs that are active against a malignancy but that have different side effect profiles should permit the use of maximal doses of more than one agent. If one is forced to lower the dose of an individual drug below a level that would be effective against a cancer in order to include that drug in a combination, then it is unlikely that the drug will add anything except side effects to the combination. Chemotherapy combinations should utilize drugs with different mechanisms of action. Because cancers are frequently composed of heterogeneous clones of cells that may express different sensitivities (or resistance) to different drugs, a combination of drugs which work by a variety of mechanisms may prevent the emergence of a clone of tumor cells that is resistant to a single agent.

Combinations of chemotherapy drugs are also often used in the treatment of cancers that are incurable. A chemotherapy combination often results in higher tumor response rates than can be achieved if the drugs in the combination are used individually. While tumor response rates do not necessarily correlate with improvement in life span, tumor shrinkage may improve quality of life by relieving symptoms caused by the tumor. However, some chemotherapy combinations have produced longer survival of patients with advanced cancers compared with using single drugs sequentially. Combinations of chemotherapy drugs, however, are more likely to cause side effects than single drugs. As mentioned previously, it is critical that physicians communicate the goals and risks of treatments clearly with patients to help make a decision about the appropriateness of combination chemotherapy in the setting of an incurable malignancy.

Evaluation of Patients After Anticancer Treatment Concludes

After cancer treatment concludes, patients may benefit from monitoring for late side effects of treatment. There are a number of long term effects of treatment that can become very bothersome or even life threatening.

For example, peripheral neuropathy after treatment with oxaliplatin may persist for years. Similarly, myelodysplasia or acute myeloid leukemia can arise years after exposure to mustard compounds or topoisomerase inhibitors. While there are no guidelines that call for close monitoring of patients for the emergence of leukemia after chemotherapy treatment, physicians need to be aware of the potential for late complications to arise.

In addition to monitoring patients for late side effects of treatment, most patients will continue to see their oncologist after treatment to be checked for possible recurrence of cancer. Many national groups have issued guidelines regarding appropriate testing and evaluation of patients after cancer treatment. In general, these guidelines are not based on evidence from clinical trials, but are the product of consensus from panels of “experts”. Nevertheless, it is probably helpful for patients to be informed at the end of treatment about the kind of monitoring they can expect to undergo.

Conclusion

Medical oncologists provide primary care for the cancer patient and also prescribe and supervise chemotherapy. Medical oncologists usually continue to see patients after their initial treatment is over, to assess for long term complications of treatment and evaluate the possibility of cancer recurrence. Medical oncologists frequently are the supervising physicians for patients with cancer who receive care in hospice.

Chemotherapy treatment should be based on the goals of care of any particular patient. When cure of a cancer is the goal of treatment, the patient and physician may be willing to accept significant side effects of treatment. When cure is not possible, chemotherapy may be given to improve quality of life by relieving symptoms of cancer and also, possibly, to prolong life. In this setting, it is important that the oncologist communicate frequently with the patient to insure that side effects of treatment not become so burdensome that they outweigh the benefit of therapy.

Chemotherapy can be given before or after definitive surgery to improve cure rates of many cancers. Chemotherapy can also be given before, after or during radiation therapy. In each of these settings, careful planning with surgeons and radiation oncologists is essential to produce a safe and effective treatment.

Thought Questions

1. In many parts of the world, chemotherapy for solid tumors is prescribed and supervised by oncologists who also supervise radiation therapy. In the United States, most gynecologic oncologists prescribe and supervise chemotherapy for their patients. What is the advantage of each approach? What are the disadvantages of each approach? Why are other organ system cancers not treated by the surgical subspecialist who operates on them? Why do radiation oncologists not administer chemotherapy in this country?

   Your answer:

Expert Answer

2. While chemotherapy can improve the cure rate of early stage breast cancers after surgery, current chemotherapy cannot cure Stage IV (metastatic) breast cancer.

   a) If chemotherapy has no effect on the curability of metastatic breast cancer, why is it possible for chemotherapy to improve cure rates of early stage breast cancer?

      Your answer:

      Expert Answer

   b) The same drugs used to treat patients with early stage breast cancer are also used to treat patients with metastatic disease. How might the stage of a patient's breast cancer affect the choice of drug doses or administration schedules?

      Your answer:

      Expert Answer

3. Using two or more chemotherapy drugs concurrently frequently results in higher tumor shrinkage (response) rates than using the same drugs individually in sequence when treating metastatic cancers. However, in a number of metastatic cancers, there is no difference in overall survival regardless of whether patients are treated with concurrent or sequential combinations of chemotherapy. What might be the reasons to choose to give a patient with a metastatic cancer two or more chemotherapy drugs concurrently or sequentially?

   Your answer:

Expert Answer

Glossary

Adjuvant chemotherapy- Chemotherapy given after primary surgery or radiation

Complete response- Eradication of all known tumor as assessed by physical exam, imaging studies such as CT or other scans, and, when indicated, biopsy of involved areas such as bone marrow

Neoadjuvant chemotherapy- Chemotherapy given before surgery or radiation

Partial response- Reduction by 50% or more of all known measurable tumors with no evidence of new tumor growth

Prophylactic cranial irradiation (PCI)- Elective irradiation of the brain to attempt to prevent the later (expected) appearance of brain metastases

Progressive disease- The appearance of new tumors or growth by 25% of existing tumors

Pyrrhic victory- A victory with devastating losses

Stable disease- A cancer that has neither demonstrates a partial response or progression

Therapeutic index- Benefit of a drug divided by the drug's toxicity

References

1. Band PR. The birth of the subspecialty of medical oncology and examples of its early scientific foundations. J Clin Oncol. 2010;28(22):3653-58.
   PubMed Abstract
2. Pearson HA. History of pediatric hematology oncology. Pediatr Res. 2002;52(6):979-92.
3. Adjuvant! Online: Decision making tools for healthcare professionals. Accessed 25 December 2010
4. National Cancer Institute (NCI). Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE). Accessed 12 November 2015.