Clinical Oncology and Chemotherapy

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Mass Effects of Malignancy

Tumors produce clinical problems as a result of local expansion, with obliteration of normal tissues as the malignant cells proliferate within the confines of the involved organ. Marrow replacement by leukemia results in reduced production of the normal cellular elements of the blood. Lung cancer compromises oxygen exchange in involved alveoli. Primary or metastatic cancer in bone causes weakness resulting in pathologic fractures. A variety of intraabdominal neoplasms can encase the ureters, causing renal failure. When neoplasia causes increased pressure on nervous tissue within the confines of the skull, the symptoms include headache and vomiting, seizure disorders, and brain dysfunction.

Treatment of these mass effects centers upon treatment of the malignancy causing the symptoms.

Paraneoplastic syndromes

Paraneoplastic syndromes result from factors released by the tumor into the bloodstream which cause clinical symptomatology. The optimal treatment for paraneoplastic syndromes is treatment of the underlying malignancy.

Metabolic Disorders

Weight loss and malnutrition

Weight loss associated with anorexia is a frequent problem in cancer management. It is often the presenting sign of malignancy. The wasting which results is known as cachexia. The cause for the disturbance remains to be determined. Abnormalities of taste and smell, physiologic malfunction of the gastrointestinal tract, excessive energy demands made by the tumor, and failure to adapt energy expenditure to the levels of nutrient intake have been implicated as causes of cachexia in patients with cancer. A polypeptide produced by macrophages has been isolated and named cachectin. This protein can cause cachexia in laboratory animals and has been found in high circulating levels in many patients with advanced malignancies. Proteolysis inducing factor (PIF) is a recently identified protein found in the serum and urine of patients with advanced cancer.

Dronabinol (Marinol®) is a cannabinoid that has demonstrated efficacy in managing cancer-related cachexia. Its effect is mediated through several central nervous system pathways, and it can also mitigate some of the chronic nausea associated with cancer and with treatment for the disease. Hallucinations
can occur, but are uncommon with the usual daily dose of 5-10 mg orally 2-4 times daily. The onset of effect can be gradual, and several days of therapy are needed before relief occurs.

**Fever**

Another sign associated with malignancy, fever is usually attributable to infection. Because of cancer-related debility, and the depression in circulating granulocytes and mononuclear cells resulting from aggressive therapeutic measures, the types of infection seen may be unusual. Infection by endogenous bacteria, fungi, viruses, and protozoa must be considered when evaluating fever of unknown etiology in patients with malignancy.

There remain unusual instances when fever cannot be explained by infection and must be attributed to a cause intrinsic to the neoplasm itself ("tumor fever"). Increased circulating levels of interleukin-1 (endogenous pyrogen) have been documented in many malignancies and may explain the fever.

**Hematologic Abnormalities**

**Anemia**

Anemia is found with increased incidence in advanced stages of malignant disease. Increased destruction of erythrocytes can result from hypersplenism, microangiopathic hemolysis, and autoantibodies seen especially in the lymphoproliferative malignancies. Anemia due to bleeding is one of the cardinal findings of gastrointestinal malignancies, especially colorectal cancers. Nutritional deficiencies due to the malignancy may result in iron deficiency. Nutritional deficits from cachexia leading to vitamin deficiency or iron deficiency may result in decreased red cell production. The anemia of chronic disease is often present as well.

**Granulocytopenia**

A decreased granulocyte count is commonly associated with marrow infiltration by hematologic malignancies and also results from chemotherapy.

**Thrombocytopenia**

The etiologies of thrombocytopenia are comparable to those associated with anemia. It should be emphasized that overproduction of any of the formed elements of the blood may occur as well.

**Coagulopathies**

Disseminated intravascular coagulation (DIC) can be caused by mucin-producing adenocarcinomas, especially those of the pancreas and stomach. It may present as migratory thrombophlebitis of unknown etiology, which can produce venous thrombosis and pulmonary embolism (Trousseau’s syndrome).

Hypercoagulable states also may be associated with marantic (nonbacterial) endocarditis and resultant thromboembolic episodes.

The treatment of the primary malignancy is the only successful therapeutic attack on the problem. Anticoagulation, following the principles for treatment of DIC, may provide short-term benefits in acute situations, but with attendant risks.

Acute promyelocytic leukemia is often associated with abnormalities of hemostasis related to a hypercoagulable state. The malig-
nant immature granulocytes can release pro-
coagulant materials that initiate DIC. In this
case, the addition of anticoagulation to the
initial phase of leukemia therapy results in an
improved chance for a successful outcome.

**Diagnosis**

There are three general goals in evaluating
a patient for a malignancy:

- Information must be gathered leading to
  biopsy of tissue to establish the patho-
  logic diagnosis of neoplasia.

- Determine the extent of tumor spread,
  both at the site of origin and as metas-
  tases. The process of obtaining this
  information is known as staging.

- Determine the effects of malignancy on
  the overall health and performance of the
  patient. This requires determination of
  the patient's performance status. The
  influence of performance status on
  prognosis is demonstrated by reports
  directly correlating the level of perfor-
  mance and median duration of survival in
  patients with inoperable lung cancer.

**Pathologic diagnosis**

Early detection depends primarily on
awareness of the hereditary and environmental
factors contributing to the incidence of cancer,
combined with thorough exploration for symp-
toms and signs that could lead to further diag-
nostic workup. The seven warning signals
widely publicized by the American Cancer So-
ciety are useful to remember and are usu-
ally covered in a review of systems. A careful phy-
sical examination is especially useful in detect-
ing early breast cancer, cancer of the colon,
skin cancer, and head-and-neck cancers.

Four diagnostic screening tests have proved of value in early cancer detection:

- The exfoliative cytology (Pap smear) screen for cervical cancer.
- Fecal occult blood testing, accompanied by periodic sigmoidoscopy.
- Mammograms.
- Digital rectal exam with blood PSA testing for prostate cancer. In 2012, the United States Preventive Services Task Force (USPSTF) questioned the value of routine screening and issued a statement that screening non-high risk men for prostate cancer was not cost effective. In response, physician groups recommend careful discussion with patients aged 50 years and older.

The prudent guidelines for early cancer
detection provided by the American Cancer
Society can be summarized as follows:

- A cancer related checkup is recom-
mended every 3 years for those 20 to 40
  years of age.

- For breast cancer screening, an exami-
nation of patients 20 to 40 years of age
  by a physician is recommended every 3
  years, a self-examination every month,
  and one baseline mammogram by the
  age of 40.

- In the 40 and over age group, a yearly
  cancer checkup is recommended by the
  American Cancer Society. Women over
  40 are advised to have a mammogram
  and a professional breast examination
ev​ery year, and a self examination every
month. There is no set recommendation
for discontinuation of mammography at
a certain age, as long as the patient re-
mains healthy. The benefit of mammo-
graphic screening of elderly patients with
multiple health issues is questionable.
Cervical cancer screening should begin at age 21. Women under age 21 should not be tested.

Women between ages 21 and 29 should have a Pap test every 3 years. Testing for the presence of human papilloma virus (HPV) should not be performed in this age group unless needed after an abnormal Pap test result.

Women between the ages of 30 and 65 should have a Pap test plus an HPV test (called “co-testing”) every 5 years. This is the preferred approach, but screening experts recognize the value of Pap smear alone every 3 years if HPV testing is not practicable.

Women over age 65 who have had regular cervical cancer testing with normal results should not be tested for cervical cancer. Once testing is stopped, it should not be started again. Women with a history of a serious cervical pre-cancer should continue to be tested for at least 20 years after that diagnosis, even if testing continues past age 65.

A woman who has had her uterus removed (and also her cervix) for reasons not related to cervical cancer and who has no history of cervical cancer or serious pre-cancer should not be tested.

A woman who has been vaccinated against HPV should still follow the screening recommendations for her age group.

For endometrial cancer, the American Cancer Society recommends that at the time of menopause, all women should be told about the risks and symptoms of endometrial cancer. Women should report any unexpected bleeding or spotting.

For colon and rectal cancer, a digital rectal examination and fecal occult blood test are recommended yearly after age 50. A sigmoidoscopic examination every 5 years or a colonoscopy every 10 years are also recommended. As alternatives to endoscopic studies, double contrast barium enema every 5 years or CT colonography every 5 years are recommended.

Discussions on prostate cancer begin at age 50. African American men, or men with a first degree relative with prostate cancer before age 65 should have should be counseled at age 45. If men decide to be tested, they should have the PSA blood test with or without a rectal exam (this is the official recommendation of the American Cancer Society).

General Concepts of Cancer Therapy

Current knowledge of cell growth suggests that there are two discernible periods of importance:

- Mitosis—when separation of nuclear material and cytoplasm occurs, resulting in two identical cells.
- The duplication of nuclear material (the S phase).

Additionally, the remainder of time is divided into two growth phases, G1 and G2. The entire period from one cell division to the next is called the cell cycle. Chemotherapy affects cells in direct relationship to how active they are in the cell cycle.
There are two general classes of cytotoxic agents:

- Cell cycle specific—only effective while malignant cells are in a certain point in the cell cycle.
- Cell cycle nonspecific—effective at any point in the cell cycle.

Other classes (hormones, biological agents) have complex and poorly understood mechanisms of action.

**Classes of Cytotoxic Agents**

**Alkylating agents**

Alkylating agents bind directly to DNA and cause cross-strand breaks which disrupt transcription and replication. Mechlorethamine (nitrogen mustard), cyclophosphamide, nitrosoureas, and platinum derivatives are examples. Most are cell cycle nonspecific.

**Antimetabolites**

These agents may compete with normal precursors for the catalytic site of key enzymes or substitute for metabolites incorporated into DNA or RNA. Methotrexate, 5-fluorouracil (5-FU), cytosine arabinoside ( Ara-C), gemcitabine, 6-mercaptopurine, and 6-thioguanine are examples. Since these agents usually work on specific enzyme systems at the cellular level, most are cell cycle specific.

**Antibiotics**

Originally developed as antimicrobials, these agents intercalate with DNA causing inhibition of transcription and replication. Some also inhibit topoisomerase II, a key protein in “DNA unfolding” required for transcription. Doxorubicin (Adriamycin), epirubicin, daunorubicin, idarubicin, actinomycin-D, and bleomycin are examples. They are cell cycle nonspecific.

**Plant alkaloids**

One of the broader classifications of cytotoxic agents, plant alkaloids are best discussed by drug class. Vinca alkaloids (vincristine, vinblastine, vinorelbine, vindesine) bind to tubulin, causing impairment of microtubule formation.

Epidophyllotoxins (teniposide [VM 26] and etoposide [VP-16])—inhibit topoisomerase II, causing single strand breaks in DNA. As a general rule, plant alkaloids are cell cycle specific.

**Hormonal agents**

- Tamoxifen—binds to (and blocks) estrogen receptors. The agent also has weak pro-estrogenic effects.
- Leuprolide, Goserelin—LHRH agonists that decrease secretion of luteinizing hormone (LH) and decreases testosterone production.
- Flutamide, Bicalutamide—bind to (and block) testosterone receptors.

**Biological agents**

- Interferons—mechanism unclear.
- Interleukins—mechanism unclear.
- Kinase inhibitors—a wide variety of agents that affect cell growth and development. They are overall well tolerated, but can cause cutaneous toxicity. Trastuzumab (Herceptin®) can cause cardiotoxicity. Additional kinase inhibitors are of use in the treatment of chronic myelocytic leukemia, melanoma, renal cell carcinoma, and myelofibrosis.
Epidermal growth factor inhibitors—erlotinib (Tarceva®) has efficacy in selected patients with non-small cell lung cancers. Cetuximab (Erbitux®), a monoclonal antibody, has demonstrated effectiveness in lung, head/neck, colorectal cancers; those colorectal cancers that express K-RAS mutant changes do not demonstrate sensitivity to cetuximab. Thus, it is possible to identify patient populations that may benefit from treatment, allowing oncologists to target therapies that are effective, and avoiding expense in other patient populations.

**Monoclonal Antibodies**

A number of directed monoclonal antibodies have been developed to target specific malignancies...

- **Cetuximab (Erbitux®)**—see above.

- **Rituximab (Rituxan®)**—directed at CD20 on lymphocytes and effective in lymphomas, chronic lymphocytic leukemia, and Waldenstrom’s macroglobulinemia.

- **Ofatumumab (Arzerra®)**—directed at CD20 on lymphocytes and effective in chronic lymphocytic leukemia.

- **Alemtuzumab (Campath®)**—directed at CD52 on lymphocytes and effective in chronic lymphocytic leukemia.

- **Ipilimumab (Yervoy®)**—is a new agent directed at CTLA-4 and is active in metastatic melanoma. Significant neurologic toxicities limit use to selected patients.

- **Pembrolizumab and nivolumab**—these are new inhibitors of the programmed cell death (PD-1) pathway, and facilitate T-cell mediated tumor cell kill. They are also known as checkpoint inhibitors. They have recently been approved for use in melanoma and in non-small cell lung cancer. Clinical trials are underway to determine their utility in concert with other agents and in other types of cancer.

**Complications of Cytotoxic Chemotherapy**

In general, chemotherapy affects cells that grow rapidly, whether normal or abnormal. Constitutional complaints such as fatigue, weakness, and lassitude occur to some degree in over 90% of patients. Anorexia may occur, but it is often difficult to tell in some cases whether it is secondary to drugs or cancer.

**Gastrointestinal**

Alkylation agents and antimetabolites are the primary culprits. Nausea and vomiting may occur but with newer antiemetic agents (ondansetron, granisetron, dolasetron), nausea and vomiting are controlled in over 85% of all patients receiving cytotoxic chemotherapy.

Diarrhea of variable severity may develop with most agents, especially 5-FU and methotrexate.

Mucositis presents as painful mouth sores (stomatitis). It is not related to infectious agents, and may involve the entire gastrointestinal tract.

Many monoclonal antibodies directed at the CD20 protein on lymphocytes may reactivate hepatitis B virus. Presence of HBV is a contraindication to the use of these agents.

**Respiratory**
Drug induced pulmonary toxicity occurs most commonly with busulfan, bleomycin, and mitomycin-C. Pulmonary fibrosis is the usual pathologic problem. Pulmonary function tests are usually abnormal (especially diffusion rate for carbon monoxide [DLCO]). In patients who will be receiving large doses of agents known to cause pulmonary toxicity baseline PFT with DLCO is done, and serial measurements are performed on treatment to follow for toxicity.

"Radiation recall" is a clinical syndrome of interstitial infiltrates in regions of lung previously irradiated when subsequent chemotherapy (especially Adriamycin) is used.

**Dermatologic**

5-FU, cisplatin, and Adriamycin all sensitize the skin to sunlight and increase the risk for sunburn.

"Hand-Foot syndrome" is seen most commonly with 5-FU. The hands and feet become painfully swollen, with subsequent desquamation.

In acral erythema the tips of the digits become erythematosus and painful. This occurs with Ara-C and 5-FU.

**Genitourinary**

The platinum containing agents are all nephrotoxic (cisplatin more so than carboplatin).

Cyclophosphamide (in high dose) and ifosfamide (at any dose) may cause hemorrhagic cystitis.

Toxicity is curtailed or avoided with vigorous hydration (for all the above agents), mannitol diuresis (for cisplatin), and the use of mesna (which binds to acrolein, a metabolic product of ifosfamide responsible for the hemorrhagic cystitis).

**Neurological**

Seizures have been reported with high dose busulfan (used in high dose chemotherapy).

Paresthesias, dysesthesias, and hyporeflexia have been reported with vinca alkaloids, taxanes, and cisplatin. Watch deep tendon reflexes closely in patients receiving these agents!

CNS disturbances such as psychoses, hallucinations, leukoencephalopathy are rare, but are increased in frequency with intrathecal chemotherapy or combined radiation to the brain and chemotherapy.

**Hematologic**

The most frequent delayed complication (5 days or more after chemotherapy). Anemia, leukopenia, or thrombocytopenia can occur with any single agent and occur to some extent with most combination agents. The possibility of neutropenic fever, bleeding, or anemia exists for every patient who receives chemotherapy. Supportive care reduces the risk involved.

Hemolytic-uremic syndrome can occur with mitomycin-C; the risk is dose related and cumulative. Most patients die of this complication. Some have reported that plasmapheresis may help.

**Miscellaneous toxicities**

Fever—VP-16, interferons, and interleukins are common culprits.
Extravasation—drugs which leak outside of the vein cause local tissue damage, increase the risk of infection, and may result in amputation. Most common with agents known as vesicants (Adriamycin, methotrexate, mithramycin). Most agents known to cause local tissue damage on extravasation are given by central vein.

Leukoencephalopathy—reported with anti-CD20 monoclonal antibodies.

**NOTE:** *This material will not be covered during the didactic lecture. It is added here as a service to the reviewer to help with preparation for the board examination.*

**Hematologic Support**

Many patients who receive chemotherapy will require some support for anemia and/or thrombocytopenia. The chance of needing hematologic support is higher for patients who receive combination chemotherapy or chemotherapy at more frequent intervals.

Packed red cells (PRBCs) are usually given if the hemoglobin is <8.0 g/dl. It may be necessary to transfuse with a higher hemoglobin if medically indicated.

Platelets are not usually transfused until the platelet count is <20,000 unless bleeding occurs before this time.

**Complications of blood product use**

Fever—this most often is not from infection, but an immune response to challenge with a foreign antigen. Many blood banks now filter leukocytes at the time of blood donation, lessening the risk of transfusion-related fever.

Hemolysis is less of a problem in cross-matched blood, but patients who have received multiple transfusions will have circulating antibodies to multiple antigens, making an exact crossmatch difficult and increasing the risk of hemolysis.

**Thrombocytopenia**—transfused platelets may be sequestered and destroyed by the spleen. This usually occurs in patients who have received multiple transfusions and have high levels of circulating platelet antibodies. This can be lessened by using single donor platelets.

**Infection**—may occur from hepatitis, HIV, or other viruses. Cytomegalovirus (CMV) can be transmitted to the patient if the patient was never exposed...in the bone marrow transplantation setting, CMV negative patients should receive CMV negative blood products.

**Neutropenic Fever**

**Definition**—temperature above 38.5°C (101.4°F) with an absolute granulocyte count (AGC) below 500 cells/cc.

Neutropenic fever is a medical emergency. The risk of death approaches 3% per hour that the fever goes untreated; there is a 100% mortality rate if not treated for three days. Of the infectious agents involved with neutropenic fever 99% are normal, indigenous flora.

In patients with indwelling central venous catheters, *S.aureus, S.epidermidis,* and *Klebsiella* species are the most common. Often, fungal infections can complicate matters. *Candida* is by far the most common pathogen, but *Aspergillus* and other fungi may be involved as well. Occasionally *Pneumocystis* and *Toxoplasma* can cause fever, but they are relatively unusual.
**Treatment of neutropenic fever**

Adequate hydration is an important initial step in management. Ensuring adequate intravascular volume lessens the risk of hypotension with the complication of organ ischemia and damage.

Intravenous antibiotics are given until the AGC is >1000, at which point it is often possible to change to oral agents if the patient is afebrile and tolerating meals without emesis. Combination intravenous regimens are preferred to single agents; in most cases one gram positive drug and one gram negative drug are used.

Colony stimulating factor support (granulocyte colony stimulating factor [G-CSF or Neupogen®]) decreases the duration of fever and neutropenia, and shortens the length of hospitalization.

Though not often considered initially, it is important to treat for presumed fungal infections if the patient is still febrile by day 5 of fever. Treatment with appropriate antifungal agents is recommended; the agent(s) selected are often empiric, as cultures often are negative.

If the AGC is <1000 no rectal exam should be performed. Microscopic tears in the rectal mucosa occur in every patient receiving a rectal exam. Because of the high coliform count in the rectum, tears in the mucosa provide a portal of entry for these bacteria. The bacteremia that results occurs in a patient who is immunocompromised and fulminant sepsis and death have occurred in these patients within 24 hours of a rectal examination.

**Pain Control and the Cancer Patient**

Pain may come from many sources. Bony metastases are probably the most painful. Additionally, compressive effects of tumor on contiguous structures and infiltration of organs may cause pain. At some point, pain is a complicating factor in over 80% of patients with cancer.

**Control of pain**

Surgery can play a valuable role in the palliation of pain. Bypass procedures for patients with gastrointestinal involvement may help avoid obstruction. Removal of local tissues affected with malignancy and debridement of necrotic debris may help reduce the risk of infection and improve patient esteem.

Radiotherapy is effective locally in pain control. In patients with isolated bony metastases radiation helps shrink tumor deposits and reduce pain. Patients with a local recurrence may achieve some degree of control with improved patient esteem.

Chemotherapy is effective systemically for pain control. It can be used for local recurrence in areas previously treated by radiation.

**Analgesics**

Non-narcotics afford relief to the vast majority of patients with cancer-related pain. NSAIDS are helpful in management of pain from some bony metastases. Acetaminophen may help alleviate minor to moderate pain. Tricyclic antidepressants are of value in management of minor pain and may bring complete relief to some. They are beneficial as an adjunct in more severe pain.

Narcotics are utilized for severe cancer pain. In most cases a fairly weak narcotic is used initially (i.e., propoxyphene). Stronger
agents are subsequently used for more severe pain.

Most cancer patients have two types of pain:

- Background pain that is always present, more or less constant level, described as “dull”, “aching”, “boring”.
- Breakthrough pain—spikes of severe, sharp pain lasting 30 minutes to several hours.

Effective management of cancer pain requires addressing both background and breakthrough pain. Initially, a single agent may cover both background and breakthrough pain. In more severe cases, use a continuous release agent (morphine, fentanyl) for background pain, and short acting agents (immediate release morphine, hydromorphone, oxycodone, etc.) as needed for relief of breakthrough pain.

The major dictum of pain relief in patients with cancer is to provide enough analgesia to allow for an acceptable functional state for the patient. Social, ethnic, racial, and concomitant disease all influence how individuals perceive pain.

Keys to effective management of cancer pain:

- Try to understand the patient’s pain. Avoid open-ended questions like “How do you feel?” and ask directed questions: “When you take the pain pills, does your pain go away completely?”, “How long does the pain relief last?”, “Does the medication make you sleepy?”, “What other side effects have you noticed that might be related to your pain medication(s)?”
- Let the patient determine when to take the pain medicine. “q 4 hours prn pain” may be inadequate for a patient with cancer. The instruction, “take as needed for pain” may work much better.
References


4. Salgia, R, Skarin, AT, Ross, ME; Small molecule epidermal growth factor receptor inhibitors for advanced non-small cell lung cancer; UpToDate Online 17.3; 2009
