K. J. Lee: Essential Otolaryngology and Head and Neck Surgery (IIIrd Ed)

Chapter 34: Cancer Chemotherapy

Malignant neoplasms are best treated by surgical removal from the body when they are sufficiently localized and well situated to allow the procedure to be done at reasonable risk and with tolerable side effects. When the tumor is relatively inaccessible, i.e. the posterior third of the tongue, or when function can be better preserved by avoiding surgery, i.e. some cases of limited carcinoma of the larynx, then radiation therapy is indicated. However, when the tumor is no longer regionally confined, or when it is known to have a high incidence of metastasis after surgery, then chemotherapy should be considered.

Modern chemotherapy is relatively new. The first patient was treated in 1943 for a lymphosarcoma, with the only chemotherapy drug then available, nitrogen mustard (mechlorethamine) (then a secret wartime drug), at the New Haven Hospital. Since that time, more than 50 individual drugs have been found effective and are in use singly or in combination. For some neoplasms, they prolong survival or provide a cure. For others, they provide palliation and prolongation of life and for some they provide only palliation with uncertain prolongation of life. Unfortunately, with the currently available drugs, some tumors have uncertain palliation (Table 34-1). The field is sufficiently complex that chemotherapy should be given by an oncologist but the otolaryngologist must understand what is being done and why.

Chemotherapy Drugs

In general, anticancer drugs interfere either with the synthesis of protein, DNA, or RNA by the cell, or they inhibit mitosis. Specific effects on the cell cycle have also been described. Drugs are classified into groups based on their characteristics or their origins.

The usual grouping is:

1. Alkylating agents.
2. Nitrosoureas.
3. Antimetabolites.
4. Mitotic inhibitors.
5. Antitumor antibiotics.
6. Miscellaneous.
7. Hormones or antihormones.

Alkylating Agents

These are highly reactive compounds that substitute an alkyl group for the hydrogen atoms of many organic molecules. The drugs cross-link the strands of DNA, preventing DNA replication and the transcription of RNA. The major site of action is the N-7 position of guanine. Most of the commonly used alkylating agents are derivatives of nitrogen mustard, like chlorambucil, cyclophosphamide, and melphalan. Busulfan is an alkyl sulfonate and thiotepa is a trifunctional alkylating agent. Some drugs seem to act like alkylating agents and are therefore grouped with them such dibromodulcitol, dacarbazine, estramustine, and cisplatin

(Table 34-2). They are effective in many tumors including lymphomas, lung, testicular and ovarian cancer, and chronic leukemias. Cisplatin has proven efficacy in testicular and ovarian carcinoma and is showing great promise in clinical trials in lung and in head and neck cancer.

Nitrosoureas

These are group of drugs that are lipid soluble and behave like alkylating agents. They can gain access to the central nervous system and other areas that require lipid solubility. They all have a chloroethyl side arm linked to a nitrosourea moiety. In addition to alkylation, they also act by carbamoylation and inhibit both DNA and RNA. They lack cross-resistance with the other alkylating agents. They have been used primarily in treatment of primary brain tumors, lymphomas, myeloma, and gastrointestinal (GI) neoplasms (Table 34-3).

Antimetabolites

These agents interfere with the biologic synthesis of DNA and RNA either by blocking enzyme pathways or by being incorporated themselves into a defective DNA.

Antimetabolites are frequently structural analogues of normal metabolies essential for cell growth and replication. Hence, they are most effective in rapidly growing tumors. They are usually divided into the pyrimidine analogues (5-azacitidine, 5-fluorouracil, hexamethylmelamine), purine analogues (6-mercaptopurine, 6-thioguanine), and the folic acid antagonists (methotrexate, triazinate). Although hydroxyurea does not look like an antimetabolite it appears to behave like one and is grouped with the antimetabolites. The primary role of the antimetabolites is in treatment of leukemias and carcinoma of the ovary, breast, stomach, pancreas, and colon (Table 34-4). Methotrexate has been the single most widely used drug for treatment of head and neck cancers that are unresectable or metastatic. It has been used both in normal dosage and in programs with high-dose and leucovorin-rescue. The only controlled clinical trial so far showed no difference in the two regimens.

Mitotic Inhibitors

These drugs have been derived from plants, either the periwinkle plant (Vinca rosea Linn) or Americal mandrake plant (Podophyllum peltatum). They bind to microtubules and cause metaphase arrest thereby inhibiting effective mitosis. They are active in leukemia, lymphoma, lung, testicle, and breast cancer (Table 34-5).

Antitumor Antibiotics

These agents have been isolated from a great variety of microorganisms in many parts of the world. They act to affect the synthesis or function of nucleic acids and especially DNA. Antimitotic and cell surface effects may occur with these agents. These drugs have a wide spectrum of activity including childhood tumors, sarcomas, leukemias, lymphomas, breast, bladder, ovary, testicle, and head and neck cancers (Table 34-6). Mithramycin also has been used for the treatment of hypercalcemia caused by malignancy.

Miscellaneous Agents

This includes those drugs that do not readily fit into one of the other group designations. Mitotane (o,p'-DDD) is used solely in the treatment of adrenal cortical carcinoma. Procarbazine has been used primarily in a four drug combination for treatment of Hodgkin's disease and other lymphomas. L-Asparaginase is unique in that it is an enzyme product that acts by inhibiting protein synthesis by depriving tumor cells of the amino acid asparagine. Since normal cells can synthesize their own asparagine, they are unaffected. Thus this is the first antineoplastic agent that is effective against some cancer cells and is not toxic to most cells. Unfortunately, the enzyme is prepared from bacteria and therefore is a foreign protein which elicits fever, an antibody reaction, and can cause rash or even anaphylaxis. It is used primarily in the treatment of childhood acute lymphocytic leukemia and must be used with extreme caution (Table 34-7).

Hormones and Antihormones

Adrenal corticosteroids have been used for a long time in the treatment of leukemia, breast cancer, and lymphoma. Estrogens, especially diethylstilbestrol and chlorotrianisene (TACE), have been used for prostatic carcinoma and occasionally for late postmenopausal patients with breast cancer. Androgens have been used in the management of breast cancer for many years. Recently, progestational agents like megestrol, hydroxyprogesterone, and medoxyprogesterone have been used in the treatment of endometrial carcinoma and renal cell carcinoma.

The antiestrogen, tamoxifen (Nolvadex), is a nonsteroidal agent that blocks the estrogen effect possibly by binding to cytoplasmic receptors. It has been effective in the majority of patients with breast cancer whose tumor was estrogen-receptor positive. It is given orally and has minimal side effects. Aminoglutethimide (Cytadren) inhibits the enzymatic conversion of precursors to adrenal gluococorticoids and mineralocorticoids, and to estrogens. In effect, it causes a "medical adrenalectomy" that is as efficacious as a surgical adrenalectomy. It has been useful in many cases of breast cancer and prostate cancer.

Chemotherapy for Head and Neck Tumors

Most primary tumors of this area are of the squamous cell type. The traditional drug of choice has been methotrexate. In recent years, promising reports have indicated efficacy for bleomycin and cisplatin. Combinations of these agents were tried and are still being tried, but so far the toxicity has been severe and hence limiting. Combined modality therapy with surgery, radiation, and chemotherapy also is being evaluated. Results are better than before, but still far from satisfactory.

Attempts at intra-arterial infusion of chemotherapy drugs has gone through cycles of popularity and disillusionment at a number of research centers. It seems clear that for better results we will need better drugs and better ideas.

Lymphomas

One of the most common tumors seen by otolaryngologists is the lump in the neck that when eventually excised or a biopsy taken is found to be Hodgkin's disease or non-Hodgkin's lymphoma. This is extremely important because most cases of early Hodgkin's disease can be cured and most non-Hodgkin's lymphomas can be effectively palliated.

Hodgkin's Disease

Hodgkin's disease should be staged according to the Ann Arbor modification of the Rye classification. Patients are divided into four stages (Table 34-8) and subclassified A (absence) or B (presence) of systemic symptoms of unexplained fever, weight loss, and night sweats.

There is general agreement that patients in stage IA, IB, and IIA should be treated with radiation therapy and have a better than 90% remission rate that is probably a cure. Patients with IIIB, IVA, and IVB disease should be treated with combination chemotherapy and can expect a 75-80% remission rate, but with 40-50% relapsing so that the overall cure rate is only 50%. There is controversy among experts on the treatment of IIB and IIIA disease with advocates of radiation therapy alone, chemotherapy alone, and combined radiation plus chemotherapy. Clinical trials are in progress to answer the question.

The "standard" chemotherapy for Hodgkin's disease is known by the acronym MOPP and consists of monthly courses of mechloretamine, vincristine (Oncovin), procarbazine, and prednisone. Patients who fail or relapse on this regiment, are usually treated with ABVD, a noncrossreactive combination consisting of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine. Frequently, these patients can be salvaged after a radiation therapy failure or the failure of the initial chemotherapy regimen.

Non-Hodgkin's Lymphoma

Although the same staging system is used (Table 34-8), it is less satisfactory than in Hodgkin's disease. The disease tends to be multifocal or spreads rapidly. Hence, only the rare stage IA patient is treated with radiation. All others are treated with chemotherapy. The pathologic classification has been in a state of flux with nomenclature changes reflecting the rapid increase in knowledge. In general, patients with nodular disease have a more indolent course and a longer survival than those with diffuse disease. Patients with predominantly lymphocytic (small round cell) disease do better than those with so-called histiocytic disease which is really large cell lymphocytic (usually not round) type disease. Although those with nodular lymphocytic disease have a long survival, they are seldom cured. Most patients with diffuse histiocytic disease have a poor prognosis, but a subset, about 20-30%, treated with aggressive combination chemotherapy, will have a long survival that may be a cure.

Twenty years ago, all patients with Hodgkin's disease were doomed to die. Now better than 90% of early cases and 50% of late cases can be cured. With the development of more knowledge and better drugs and drug combinations, better combined modality therapy of surgery, radiation, and chemotherapy, it is only a matter of time until we will be able to cure most malignancies. It is our hope that that day will arrive sooner rather than later.

Table 34-8. Ann Arbor Staging System of Hodgkin's Disease

Stage I

Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE).

Stage II

Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE).

Stage III

Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by localized involvement of extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIISE).

Stage IV

Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

Subclassification: A for absence or B for presence of (a) unexplained weight loss of more than 10% of body weight; (b) unexplained fever above 38°C; and (c) night sweats.

Pathologic staging: Designate + for positive; - for negative by biopsy; N for lymph node; H for liver; S for spleen; L for lung; M for marrow; P for pleura; O for bone (osseous); D for skin (dermis).