Clinical Oncology

临床肿瘤学

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Preface

Clinical oncology is an important subject to medical students because cancer is a common and frequently occurring disease in clinical work. Furthermore, most doctors are experiencing the rapid advancement in both laboratory and clinical science that is occurring in clinical oncology. In order to introduce the knowledge of oncology to medical students and people who are interested in it, we edit this textbook.

This textbook is composed of 16 chapters that are organized by two major sections. The first section mainly focuses on the fundamental concepts and major basic knowledge about cancer, including "Oncology introduction ", "Anticancer drugs ", "Diagnostic radiology and ultrasonography in oncology", "Diagnosis and treatment of tumor by endoscopy", "Surgical oncology: general issues" , "Cancer chemotherapy", "Radiation oncology: general issues" and "Cancer pain management". Knowledge of these basic concepts is essential for understanding the general issues about cancer. The second section introduces the common cancer occurring in China, which includes "Nasopharyngeal carcinoma", "Lung cancer", "Breast cancer", "Primary liver cancer", "Gastric adenocarcinoma", "Colorectal adenocarcinoma", "Cervical cancer" and "Lymphoma". The particular emphasis of this section is kept on the diagnosis and treatment of cancer. Our goal is to provide a textbook that is the most useful, understandable, attractive and thorough in presenting the principles of clinical oncology. It is meant to be equally useful to students and trainees.

Due to our limited capabilities, mistakes are probably inevitable during the writing and editing. We sincerely hope that our readers will provide us with their comments and suggestions, so that we can further improve this book in its future editions.

Contents

Chapter One
Oncology Introduction

Ⅰ. History and Development of Oncology

The treatment and research for tumor may begin from the time when Human diseases occurred as well as tumor. As a primary way for cancer treatment, surgery has been used for about 200 years. In the 1920s, the first deep X-ray machine created a tumor radiotherapy; treatment of lymphoma with nitrogen mustard during World War II, which ushered in a new era of cancer chemotherapy.

In November 1969, the National Cancer Prevention and Control Research Office was established by China's Ministry of Health, which marked the beginning of standard times of cancer prevention and research. It organized and guided China's cancer prevention and control in high risk area, and carried out the integrated control and research on the cancer etiology, early diagnosis, early treatment and prevention. It carried out retrospective sampling survey of the national population based on tumor causes of death. It is responsible for organization and implementation of scientific and technological research projects, and the formulation of the national plan for cancer prevention and control research. In order to adapt to the demands of tumor development, it is responsible for organizing books written, such as *Practical Oncology*, *Diagnosis and Treatment Standards for Common Malignant Tumors*, *Standards of Classified Management in Cancer Hospital*, *Instruction Manual for the Cancer Registration in China*.

In December 1971, *The National Cancer Act* which was signed by the President of United States Richard Nixon was considered to be the formal human declaration of war on cancer. Since then, cancer treatment and research have entered a rapid development stage. Now, surgery, radiotherapy and chemotherapy are still the current three major means of cancer treatment. In recent years, the rise of biological therapy has shown its vitality. Gene therapy has also been in great expectations and breakthrough progress on tumor treatment is expected.

China Academy of Chinese Medical Oncology originating from the ancient Shang and Zhou period, has experienced Yin and Chou Chih early stage of Sui and Tang dynasties, formative stage during the Song and Yuan, and Ming and Qing periods of maturity.

Development stage is in modern. The current Chinese medicine in preventing and treating tumor has made remarkable achievements.

Ⅱ. The Growth Pattern of Tumors, the Distinction between Benign and Malignant Tumor

1. The growth pattern of tumors

Tumors often show three kinds of growth pattern, the expansive growth, exophytic growth and invasive growth.

(1) Expansive growth: Most benign tumors grow in this way. Most benign tumors grow slowly and are generally self-contained, not invading peripheral tissues and organs. It is usually nodular growth, with a complete capsule and has a clear boundary with the surrounding tissue. It can affect adjacent organs by pressing. In general, it does not obviously damage the organ's structure and function. It can be removed by surgery and recurrence is not common.

(2) Exophytic growth: The tumors which occur in body surface, body cavity and pipe organs (such as gastrointestinal, urinary and reproductive tract) often grow outside or into cavity and lumen, and form papillary, polypoid and cauliflower-like masses. Both benign and malignant tumor can show exophytic growth, but malignant tumors take invasive growth on the bottom while exophytic growth is shown. The malignant tumors of exophytic growth are easy necrosis and form malignant ulcer because of rapid growth and insufficient blood supply.

(3) Invasive growth: Cancer tissue grows and invades the adjacent tissue space, muscles, tendons, fascia, nerves, blood vessels and lymphatic vessels; capsule are generally not formed. Both carcinomas and sarcomas are in this growth pattern.

2. The distinction between benign and malignant tumor

Benign tumor: Benign tumors remain localized. They are slowly growing lesions which do not invade the surrounding tissues or spread to other sites in the body. Benign tumors in solid organs are typically well circumscribed, often surrounded by a fibrous capsule. In general, a benign tumor is usually not fatal harm and benign tumors usually grow slowly. They can usually be removed and in most cases they never come back. However, if a benign tumor is big enough, the size and weight can press on nearby organs, blood vessels, and nerves and thus cause problems.

Malignant tumor: The opposite of benign is malignant. Malignant tumors are

cancer, where the cancer cells can invade and damage tissues and organs near the tumor. Also, cancer cells can break away from a malignant tumor and enter the lymphatic system or the bloodstream. This is how cancer spreads from the original tumor to form new tumors in other parts of the body (also known as metastasize).

The ultimate criterion is the clinical behavior.

The principal characteristics of benign and malignant tumors are summarized in Table 1-1.

Table 1-1 Identification between benign and malignant tumors

Features	Benign Tumor	Malignant Tumor
Gross appearance	Circumscribed or well-defined capsule	Infiltrating the borders of lesions and no capsule
Histologic differentiation	Good	Poorer, pleomorphic cells
Mitotic figures	Less	More
Growth speed	Slow	Relatively rapid
Growth pattern	Expansion	Infiltration
Secondary change	A few	Bleeding and necrosis
Metastasis	No	Often
Recurrence	A few	Often
Effects on host	Compression, obstruction	Compression, obstruction, bleeding, necrosis, infection, cachexia, etc.

Borderline tumor: Tumor growth and biologic behavior classification are intermediated between benign and malignant tumors.

Ⅲ. Local Invasion and Metastasis

1. Local invasion

A benign neoplasm remains localized at its site of origin. It dose not have the capacity to infiltrate, invade, or metastasize to distant sites, as malignant neoplasms do. For example, as fibromas and adenomas slowly expand, most of them develop an enclosing fibrous capsule that separates them from the host tissue. However, not all benign neoplasms are encapsulated. For example, the leiomyoma of the uterus is discretely demarcated from the surrounding smooth muscle by a zone of compressed and attenuated normal myometrium, but there is no well-developed capsule.

Cancers grow by progressive infiltration, invasion, destruction and penetration of

the surrounding tissue. They do not develop well-defined capsules. The infiltrative mode of growth makes it necessary to remove a wide margin of surrounding normal tissue when surgical excision of a malignant tumor is attempted.

Surgical pathologists carefully examine the margins of tumors which was resected to ensure that they are devoid of cancer cells (clean margins). Next to the development of metastases, local invasiveness is the most reliable feature that distinguishes malignant tumors from benign tumors.

2. Metastasis

The term metastasis connotes the development of secondary implants discontinuous with the primary tumor, in remote tissues.

Not all cancers have equivalent ability to metastasize. At one extreme are basal cell carcinomas of the skin and most primary tumors of the central nervous system are highly invasive in their primary sites of origin but rarely metastasize. Approximately 30% of newly diagnosed patients with solid tumors (excluding skin cancers other than melanomas) present with clinically evident metastases. An additional 20% have occult (hidden) metastases at the time of diagnosis.

Malignant neoplasms disseminate by one of three pathways : (1) lymphatic spread, (2) hematogenous spread, or (3) seeding within body cavities.

Lymphatic spread is more typical of carcinomas, whereas hematogenous spread is favored by sarcomas. There are numerous interconnections, however, between the lymphatic and vascular system, and so all forms of cancer may disseminate through either or both systems.

A "sentinel lymph node" is defined as the first lymph node in a regional lymphatic basin that receives lymph flow from a primary tumor. It can be delineated by injection of blue dyes or radiolabelled tracers. Biopsy of sentinal lymph nodes allows determination of the extent of spread of tumor, and can be used to plan treatment.

With hematogenous spread, the blood-borne cells follow the venous flow draining the site of the neoplasm, with tumor cells often stopping in the first capillary bed they encounter. Since all portal area drainage flows to the liver, and all caval blood flows to the lungs, the liver and lungs are the most frequently involved secondary sites in hematogenous dissemination.

Spread by seeding occurs when neoplasms invade a natural body cavity. This mode of dissemination is the particular characteristic of cancers of the ovary, which often cover the peritoneal surfaces widely.

The implants literally may glaze all peritoneal surfaces and yet not invade the underlying parenchyma of the abdominal organs.

Ⅳ. Etiology of Cancer

Genetic damage is the key of carcinogenesis. What agents inflict such damage? Three kinds of carcinogenic agents can be identified: (1) chemicals, (2) radiant energy, and (3) microbial agents. Chemicals and radiant energy are documented causes of cancer in humans, and oncogenic viruses are involved in the pathogenesis of tumors in animal models and at least in some human tumors.

1. Chemical carcinogens

More than 200 years ago, the London surgeon Sir Percival Pott correctly attributed scrotal skin cancer in chimney sweeps to chronic exposure to soot. Subsequently, hundreds of chemicals have been shown to be carcinogenic in animals. Some of the major agents are presented as follows:

(1) Direct-acting agents

Direct-acting agents require no metabolic conversion to become carcinogenic. They are in general weak carcinogens but are important because some of them are cancer chemotherapeutic drugs (alkylating agents) that have successively cured, controlled, or delayed recurrence of certain types of cancer (e. g. leukemia, lymphoma, Hodgkin lymphoma and ovarian carcinoma), only to evoke later a second form of cancer, usually leukemia.

(2) Indirect-acting agents

The designation indirect-agent refers to chemicals that require metabolic conversion to an ultimate carcinogen before they become active. Some of the most potent indirect chemical carcinogens—the polycyclic hydrocarbons—are present in fossil fuels. For example, benzoapyrene and other carcinogens are formed in the high-temperature combustion of tobacco in cigarette smoking. These productions are implicated in the causation of lung cancer in cigarette smokers. Polycyclic hydrocarbons may also be produced from animal fats during the process of broiling meats and are present in smoked meats and fish. The principal active products in many hydrocarbons are epoxides, which form covalent adducts (addition products) with molecules in the cell, principally DNA, but also with RNA and proteins.

The aromatic amines and azo dyes are another class of indirect-acting carcinogens. Before its carcinogenicity was recognized, β-naphthylamine was responsible for a 50-fold

increased incidence of bladder cancers in heavily exposed workers in the aniline dye and rubber industries. Aflatoxin B1 is a strong correlation to the incidence of hepatocellular carcinoma in some parts of Africa and China.

2. Radiation carcinogenesis

Radiation, whatever its source (UV rays of sunlight, X-rays, nuclear fission, radionuclides) is, is an established carcinogen.

3. Viral and microbial oncogenesis

Many DNA and RNA viruses have proved to be oncogenic in animals as disparate as frogs and primates. However, only a few viruses have been linked with human cancer. Oncogenic RNA Viruses. Human T cell leukemia virus-1(HTLV-1) is the only retrovirus that has been demonstrated to cause cancer in humans. Oncogenic DNA Viruses. Several oncogenic DNA viruses that cause tumors in animals have been identified.

①Human Papillomavirus. Some types of HPV(e. g. 1, 2, 4 and 7) definitely cause benign squamous papillomas (warts) in humans. By contrast, high-risk HPVs(e. g. 16 and 18) have been implicated in the genesis of several cancers, particularly squamous cell carcinoma of the cervix and anogenital region. ②Epstein-Barr virus. EBV has been implicated in the pathogenesis of several human tumors: Burkitt lymphoma, nasopharyngeal carcinoma and so on. ③Hepatitis B and Hepatitis C Viruses. The epidemiologic evidence linking chronic HBV and hepatitis C virus(HCV) infection with hepatocellular carcinoma is strong. It is estimated that 70% to 85% of hepatocellular carcinomas worldwide are due to infection with HBV or HCV.

Helicobacter pylori: H. pylori infection is implicated in the genesis of both gastric adenocarcinomas and gastric lymphomas.

Ⅴ. Overview of Tumor Pathogenesis

Cancer is a multiple step event. The following makes an overview.

Oncogenes or cellular oncogenes(c-onc): they have the potential of promoting malignant transformation of cells when their activities are abnormally activated or increased. It has been suggested that neoplastic transformation occurs as a result of activation(or derepression) of growth promoter genes(proto-oncogenes), or inactivation or loss of suppressor genes.

Activation and inactivation may occur through several mechanisms: (1) mutation;

(2)translocation to a different part of genome;(3)insertion of an oncogenic virus at an adjacentsite;(4)amplification;(5)introduction of viral oncogenes;or (6) derepression.

Tumor suppressor gene:p53 is one of the most frequently mutated and extensively studied genes in human cancers. The normal functions of p53 are :(1)repair of the damaged DNA before S-phase in the cell cycle by arresting the cell cycle in G1 until the damage is repaired;(2)apoptotic cell death if there is extensive DNA damage. With loss or mutation of p53 along with damage DNA, cells undergo mitotic replication rather than apoptotic death.

The role of inheritance in oncogenesis: The evidence now indicates that for many types of cancer, including the most common forms, there exist not only environmental influences but also hereditary predispositions.

(1)Inherited cancer syndromes: Inherited cancer syndromes include several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor. The predisposition to these tumors shows an autosomal dominant pattern of inheritance. Individuals who inherit the autosomal dominant mutation have, at birth or soon thereafter, innumerable polypoid adenomas of the colon, and virtually 100% of patients develop a carcinoma of the colon by the age of 50.

(2)Familial cancers: Virtually all the common types of cancers that occur sporadically have been reported to occur in familial forms. Examples include carcinomas of colon, breast, ovary. The transmission pattern of familial cancers is not clear.

Immune surveillance: About 5% of individuals with congenital immunodeficiencies develop cancers. Analogously, immunosuppressed transplant recipients and patients with acquired immunodeficiency syndrome have increased the numbers of malignancies. It should be noted that most (but not all) of these neoplasms are lymphomas, often lymphomas of activated B cells. But most cancers occur in individuals who do not suffer from any overt immunodeficiency.

Ⅵ. Overview of Treatment and Prognosis of Tumor

1. Overview of tumor treatment

Surgery, chemotherapy and radiation are still the three main means for tumor treatment.

(1)Surgery

For most solid tumors, surgical therapy are most preferred, the most commonly used, or even unique treatment measures with some tumors, far superior to curative

effect of radiotherapy and chemotherapy alone. For most benign tumors, recurrence is rare after surgical resection. Surgical treatment is the most effective means for early and medium cancer is also involved in some comprehensive treatment in patients with advanced tumors. It has a prior right to choose in the treatment of most solid tumors, and owns important status and value. Principles of surgical treatment of tumors is the maximum removal of tumor tissues and also the maximum preservation of organs and the body's normal function. Surgical treatment has some limitations, especially for invasion or metastasis of patients. The times has become the past that operation was the only treatment. By now surgical therapy of tumor is an integrated treatment combined with traditional surgery, tumor molecular biology, endoscopic surgery and transplant surgery.

(2)Chemotherapy

Chemical therapy, also referred to as chemotherapy, is one of the methods commonly used in the treatment of cancer. It has three main characteristics: ①One is the increasing types of drug. There are dozens commonly used of drugs. ②Second is the continuous improvement in effect. Owe to the accumulated clinical experience as well as to the deep understanding on cancer, chemotherapy has been gradually transferred from palliative treatment to cure. ③Third is the continuous improvement of medication methods. In the past dominated by systemic medication, now local treatment had been used for some cancers, so the drug effect can give full play without causing systemic side effects. It is not only reducing drug use and cost, but more importantly, reducing the toxic side effects on the human body.

The biggest drawback of chemotherapy for cancer is the poisonous side effects. Firstly, it not only kills cancer cells, but also kills human cells in normal tissues, especially the hematopoietic and immune system. When white blood cells drop $4000/mm^3$, the use of Anticancer drugs must be stopped. It is the reason why some patients do not successfully finish treatment course and do not get the therapeutic effects. Secondly, cancer cells develop drug resistance, reducing the effectiveness of anticancer drug.

Tumors medical treatment strategies are as follows: ①combating and killing cancer as much as possible in the early period, while paying attention to the protection of body health; ②primarily focusing on the restoration of bone marrow and immune function after tumor load greatly reduced, as well as carrying out anticancer treatment; ③turning to focus on antitumor again, and as far as possible to eradicate residual tumor; ④long-term supporting treatment.

Treatment principle of chemotherapy is a comprehensive treatment, reducing tumor load and clearing the remaining tumors. Medication principles is according to cell prolif-

eration cycle, dividing into cell proliferation specificity drug and non-specific drug. Anti-tumor drugs include the following categories: ①interfering with cancer cell nucleic acid synthesis; ② binding DNA directly, affecting its structure and function; ③ interfering with protein synthesis; ④changing body hormone balance and inhibition, such as anti-estrogen anti-androgen and anti-adrenal cortical hormone; ⑤being often drug combination.

(3) Radiation

Radiation therapy is to kill cancer cells by the use of rays. Approximately 70% of cancer patients need radiation treatment. Some cancers can be up to radical cure by radiotherapy. For some cancer patients who are not suitable for surgical therapy or have missed surgical opportunities, or have suspicious residual tumors after surgery, radiation treatment is the important choice for the local control.

Radiation therapy is based on the following policies:

①Radical radiotherapy: when the tumor is limited or only near the organization violated or lymph node metastasis and is more sensitive radiation. Radiotherapy can be used as a means of radical treatment.

②Palliative radiotherapy: patients with advanced cancer, or who cannot undergo surgery and chemotherapy because of various reasons, radiotherapy can alleviate the symptoms, relieve suffering and prolong patients' lives.

③Preoperative radiotherapy: preoperative radiotherapy improves tumor resection rate, reducing implantation metastasis during surgery and recurrence rates.

④Postoperative radiation therapy: for some patients with residues and lymph node metastasis after tumor resection and with the presence of subclinical lesion, the rate of local control can be increased by postoperative radiotherapy.

⑤Intraoperative radiation therapy: it is the way that a large doses of radiotherapy is used directly at the tumor during the intraoperative time, which aimed at reducing postoperative recurrence rate and giving large doses for the area that may not be complete excision of regional, and often used for gastric cancer, pancreatic cancer, rectal cancer and brain tumor.

2. Prognosis of Tumors

With the development of medical science and technology, the continuous improvement of surgery, chemotherapy and radiotherapy, and development as well as the emergence of targeted therapy, tumor treatment effect then have got great improvement. Prognosis with cancer patients is improved, which prolongs lifetime and improves the quality of life.

Prognoses of tumors are related to the following factors:

(1)Type and degree of differentiation, tumor pathology: with a tumor, the poor differentiation and high malignancy, the poor prognosis, the high differentiation and low malignancy, the prognosis is good.

(2)The clinical stage of tumor: the early stage, the little probability for metastasis and more opportunities for radical, so the prognosis is better, vice versa.

(3)The tumor size has some meaning on prognosis when the size is below a certain range. This is not the most important. Some data indicates that the five-year survival rate of patients with stomach cancer or liver cancer is not much different when the size of tumors is more than 2 cm. In lung cancer, the five-year survival rate is a little higher when the size of tumors is smaller than 3 cm. There is no significant difference when it is bigger than 3 cm.

(4)Tumor invasion and metastasis are very important on the prognosis. The deeper and wider of local infiltration, the worse the prognosis; infiltration degree is positively related to prognosis. Patients with distant metastases are related to poor prognosis.

Lymph node metastasis has great influence on prognosis. It is usually considered the most important prognostic factors. Studies have shown that, for gastric cancer without lymph node metastasis, five-year survival rate is 46.2%, but only 11.6% with lymph node metastasis. Moreover, the number of lymph node metastasis is positively related to prognosis. In breast cancer, for example, the five-year survival rate without lymph node metastasis is 74.5%, 1～2 lymph node-positive 58.7%, 3 or more 35.8%, and over 7 lymph node-positive is lower than above.

(5)Tumor stromal reaction: cancer stromal reaction refers to the response resulting from lymphocytes, plasma cells and connective tissue surrounding carcinoma. Studies indicate that circumjacent area around the cancer is not clear and the prognosis is poor; if clear, it is relatively good prognosis. Lymphocyte reaction degree is inversely related to prognosis. The stronger the reaction, the better the prognosis. Cancer around is not clear enough, poor prognosis; if clear, relatively good prognosis.

(6)The importance of first treatment: if the first treatment achieves radical cure, prognosis is good. If not radical and there are remaining cancer cells in body, it will easily relapse, and prognosis is poor.

(7)The psychological status of patients: psychosocial factors are very important to the tumor occurrence, development, treatment and prognosis. The prognosis will be good with confidence, optimism and close collaboration with doctor.

Chapter Two
Anticancer Drugs

Ⅰ. History of Anticancer Drugs and Future Trend of Development

1. History of drug discovery

Chemotherapy has its origins in the work of Paul Ehrlich, who coined the term in reference to the systemic treatment of both infectious diseases and neoplasia. Many of Ehrlich's concepts regarding the experimental evaluation of new therapies using murine or rat models have survived to the present day and have provided a number of important biologic insights that have heen successfully applied to the clinical setting. Although the concept of treating cancers with drugs can trace back several centuries, there were no examples of truly successful systemic cancer chemotherapy until the 1940s. Gilman and Philips conducted the first clinical trial of nitrogen mustard in patients with malignant lymphomas at Yale University in 1942. The use of nitrogen mustard as a chemotherapeutic agent was suggested by the serendipitous findings of marrow and lymplioid hypoplasia in seamen exposed to mustard gas following the explosion of a ship containing material manufactured for use in chemical warfare in World War II. This supported previous evidence of a systemic lympholytic effect from alkylating agents of this type. The dramatic regressions of the lymphomas noted in this original study generated tremendous excitement for this new field of medicine, although enthusiasm was dampened by the fact that regrowth of tumor seemed inevitable. The results, initially published in 1946, could be said to mark the beginning of modern chemotherapy.

This same combination of "experiments of nature" and the observations of well-trained scientists have yielded a number of other important leads in the search for improved cancer therapy. This includes, among others, the recognition by Farber et al. of the importance of folates in cell growth in acute leukemia in children and the subsequent development of the first antifolate antimetabolites. This class of compounds produced perhaps the first examples of drug-induced cures of a metastatic cancer in gestational choriocarcinoma, and they remain in wide clinical use today. For their recognition of the importance of nucleic acid synthesis to inhibition of cell growth and for the development of effective antipurine analogues for cancer and other diseases, Elion and Hitchings were

awarded the Nobel Prize in Medicine in 1988. Serendipity has also played a role in the recognition of the potential of vinca alkaloids, epipodophyllotoxins and platinum coordination complexes as chemotherapy agents. This scenario has been repeated with sufficient frequency that drug discovery programs such as that of the National Cancer Institute have extensively used the approach of mass screening of natural products, as well as synthetic compounds, to identify lead compounds with potent antitumor activity and unique mechanisms of action.

Screening is key to the process of drug development because it narrows the enormous number of candidate drugs to a more manageable number for further study and possible clinical evaluation. Traditionally, this screening system has used transplantable murine tumors to search for evidence of biologic activity. Although this system identified a series of compounds for clinical trial, there was continued uncertainty regarding the relevance of these murine cell lines to human cancers. The current screening system employs a panel of human cancer cell lines grown in culture that represent the major histologic subtypes and sites of origins of human cancer. It is also possible, and probably important, to include cell lines that express various drug resistance phenotypes, such as multidrug resistance (MDR), to evaluate new agents against tumor cells manifesting these potentially clinically important cellular characteristics. Importantly, it has also been possible to automate the testing of candidate drugs in this system so that high-volume screening can be maintained. Since this screening system uses human cancer cell lines, it is expected that it will identify agents with unique promise against advanced solid tumors that can not be identified using other methods.

The history of cancer chemotherapy and of the discipline of medical oncology has been that of drug discovery. The pioneering discoveries of the early days of chemotherapy have allowed the development of a paradigm for drug discovery that persists with modifications to the present day. However, this organized approach to random screening of large numbers of compounds must be complemented in the drug development effort by attempts to exploit new therapeutic targets identified in ongoing basic cancer research. When a putative target is identified based on its biologic significance in the cancer cell, this strategy suggests that the ability of potential therapcutic agents to interact with this target and to inhibit or modify its function should be evaluated as a primary screening procedure. This mechanism-based screening is often performed in simple cell-free systems in which the target and effector are isolated. Drugs identified as promising candidates by this mechanism-based approach to drug development will also require the test systems that have been developed to validate their biologic activity in whole cells and ex-

perimental animal tumor models. Active new agents are needed for the treatment of all common human cancers. The ongoing work in drug development is crucial if our use of chemotherapy is to continue to improve and its role in potentially curative therapy is to expand. A number of promising and novel strategies are being considered for clinical trials, including antiangiogenesis factors, drugs that affect intracellular signaling pathways, differentiating agents, agents that affect a cell's ability to undergo apoptosis, and gene-specific therapies such as antisense oligonucleotides and ribozymes. These approaches, and others which will undoubtedly follow, offer great promise for the future of cancer treatment.

2. Future trend in drug development

(1)New categories of agents

Apart from traditional cytotoxic agents, which at present are still the predominant class of drugs used to treat cancer, there are several newer classes of agents and strategies that are quickly entering the clinical arena. Of note, several products of biotechnology, including the first two monoclonal antibodies and recombinant cytokines or growth factors, are listed for clinical use in the previous section. In addition, some agents with unique mechanisms of action, including retinoids and the hypomethylating agent 5-azacytidine, are also in clinical use. Otherwise, these agents are for the most part still in development. They include differentiation agents, antiangiogenesis agents, signal transduction inhibitors, monoclonal antibodies, gene therapy stratetgies and vaccines.

(2)Differentiating agents

Several classes of compounds have potent in vitro and in vivo differentiating effects on the malignant cell phenotype. This list includes the retinoids, vitamin D analogues, cyclo-oxygenase inhibitors, and the hypomethylating agent deoxyazacytidine. Unfortunately, these agents generally do not eliminate the malignant clone or affect its genotype, and thus may have only transient effects. Their role in chemoprevention is promising, as is the role in potentially aftecting favorably the natural history of incurable malignancies.

(3)Antiangiogenesis agents

Solid tumors require an adequate blood supply to grow and metastasize. They must stimulate neovascularization in order to obtain oxygen, micronutrients, growth factors and eliminate waste products. Primary or metastatic tumors that do not facilitate their own blood supply do not grow, and may regress completely or remain dormant. Bulky tumors that outgrow their blood supply undergo central necrosis. The molecular basis