Position Paper

Curative Cancer Chemotherapy

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ABSTRACT

Cancer chemotherapy provides variably effective treatment for the majority of forms of human cancer and curative treatment for some 12 categories of cancer. Curative treatment is defined as the proportion of patients who survive beyond the time after which the risk of treatment failure approaches zero, i.e., the disease-free survival plateau. This progress has resulted from a closely integrated scientific effort, including drug development, pharmacology, preclinical modeling, experimental design with respect to clinical trials, quantitative criteria for response, and a series of clinical trials (initially in children with acute lymphocytic leukemia) in which the importance of complete remission, of dose and schedule, of sequencing chemotherapeutic agents, of pharmacological sanctuaries, and particularly of combination chemotherapy was studied. The principles derived from these studies, particularly those relating to combination chemotherapy, resulted in curative treatment for disseminated Hodgkin's disease, non-Hodgkin's lymphoma, pediatric solid tumors, testicular cancer, and limited small cell lung cancer. Many patients with certain stages of solid tumors, such as breast cancer and osteogenic sarcoma, are at high risk of having disseminated microscopic disease. Experimental studies indicate that treatment which is only partially effective against macroscopic disease is much more effective against microscopic tumors. Therefore chemotherapy is administered immediately following control of the primary tumor in patients at high risk of having disseminated microscopic disease, a treatment known as adjuvant chemotherapy. This program has been highly successful in increasing the cure rate in patients with pediatric solid tumors and in prolonging disease-free survival in patients with premenopausal breast cancer. Given dissemination of the technology, it is estimated that 15,000-30,000 patients per year are potentially curable in the United States. Curability of cancer by chemotherapy only; (b) adjuvant chemotherapy; and (c) neoadjuvant chemotherapy. The term "cure" is a sensitive one and subject to several definitions. In a strict sense, a representative sample of patients with a given disease must survive a normal life span. In an operational sense, this would be counterproductive, since it would take, for example, 60 years to determine whether a given treatment program for childhood leukemia was curative. Some physicians deliberately avoid using the word "cure," preferring the expression "long-term disease-free survival." We think this inappropriate if the evidence for cure is compelling (see below). The well-being and compliance of patients are substantially improved if they are aware that they are being treated with curative intent. To the extent that physicians and investigators are ambivalent with respect to the use of the term "cure," patients and the medical community will be skeptical. One of the obstacles to progress in cancer therapy generally and in cancer chemotherapy specifically has been the presence of such skepticism.

INTRODUCTION

This paper will describe the major conceptual and clinical investigational advances that have led to the cure of certain forms of cancer by chemotherapy. Basic science has contributed to this progress in terms of the synthesis, development, and preclinical studies of the active chemotherapeutic agents. However, the major thrust of this presentation will deal with the integrated clinical and basic science efforts that have taken these tools (active chemotherapeutic agents) and constructed progressively effective and finally definitive treatment for a number of neoplastic disease categories. It will be organized primarily by disease category, historical sequence, and three strategies: (a) chemotherapy only; (b) adjuvant chemotherapy; and (c) neoadjuvant chemotherapy.

The term "cure" is a sensitive one and subject to several definitions. In a strict sense, a representative sample of patients with a given disease must survive a normal life span. In an operational sense, this would be counterproductive, since it would take, for example, 60 years to determine whether a given treatment program for childhood leukemia was curative. Some physicians deliberately avoid using the word "cure," preferring the expression "long-term disease-free survival." We think this inappropriate if the evidence for cure is compelling (see below). The well-being and compliance of patients are substantially improved if they are aware that they are being treated with curative intent. To the extent that physicians and investigators are ambivalent with respect to the use of the term "cure," patients and the medical community will be skeptical. One of the obstacles to progress in cancer therapy generally and in cancer chemotherapy specifically has been the presence of such skepticism.

For most categories of tumors, the cure rate can be securely and operationally defined as the disease-free survival plateau (69, 168). Thus following potentially definitive treatment, the risk of relapse is major at an early stage and decreases with time; then there is a point in time (1 to 4 years, depending upon the kinetics of the tumor) after which the risk of relapse is minimal (<10%). Thus the disease-free survival from that point is essentially flat (plateau). Confidence in the delivery of curative treatment by this definition is based on the number of patients and the duration of survival on that plateau. Breast cancer is the only major exception to the application of this operational definition for cure. This is because the risk of failure in breast cancer, while it decreases with time, continues beyond 5 and even 10 and 15 years (93). Thus except for breast cancer, the disease-free survival plateau will define cure in this paper.

While declining mortality from a tumor must be the ultimate parameter of curative treatment, its operational utility is limited. Thus the time required from the introduction of curative treatment for a given tumor to the recognition and confirmation that curative treatment has, in fact, been delivered is substantial. Additional time is required for the transfer of such technology to the community such that a decrease in mortality occurs. For example, curative combination chemotherapy for Hodgkin's disease

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was introduced in 1963 (37, 62). Since the risk period for failure after treatment of Hodgkin’s disease is 4 years, it was 7 years (1970) before the first full publication appeared which indicated the probability that Hodgkin’s disease was curable by chemotherapy (38). Further follow-up of that study and other studies provided extension and confirmation of the results so that, by the mid-1970s, it was generally appreciated that patients with disseminated Hodgkin’s disease could be treated with curative intent. However, not until the mid-1970s and later was there a significant decline in mortality for Hodgkin’s disease based on national mortality statistics. This time lag was shorter for testicular cancer, which is a more dynamic disease; i.e., the disease-free survival plateau begins as early as 1 year following treatment. The time lag is much longer for diseases such as breast cancer, ovarian cancer, and small cell lung cancer, wherein the dynamics of the disease are much slower and/or the cure rates attributable to chemotherapy substantially lower. It is not surprising, therefore, that in the main the curative treatment which developed between 1970 and 1975 may not yet have had an impact on national mortality statistics. Indeed, curative treatment developed after that time and, particularly after 1980, might not yet be wholly recognized as such because there has been insufficient time for the development of a secure disease-free survival plateau (60).

CHEMOTHERAPY

Gestational Choriocarcinoma

This tumor produces a marker, HCG, in the serum, which in the individual patient is a precise measure of tumor burden, including microscopic tumor burden, down to as few as perhaps 1000 cells. It was observed in the 1950s that antifolates interfered with the estrogen effect on the oviduct and that serum human chorionic gonadotropin decreased in a patient receiving methotrexate (98, 119).

In 1956, after a pilot clinical pharmacological study was observed to diminish HCG, an intensive intermittent methotrexate program was developed for gestational choriocarcinoma (119). A prompt decrease in human chorionic gonadotropin followed by a decrease in tumor size was observed in the first and subsequently in almost all patients. As complete clinical remissions were achieved, treatment was continued in an effort to reduce the microscopic tumor burden. This could be measured by serum HCG levels and such treatment was continued for one to two courses beyond the point where the HCG had reached normal levels (99, 118).

This observation has been widely confirmed, and currently methotrexate alone, or more commonly methotrexate combined with actinomycin D, produces cure rates in over 90% of patients with low or intermediate tumor burdens at the time of diagnosis. Even in patients with high tumor burden, as measured clinically, radiographically, and by tumor markers, cure rates of greater than 60% can be achieved in the majority of cases (118, 156).

A benign, but potentially malignant, precursor of choriocarcinoma is the hydatidiform mole, which when locally invasive in the uterus requires hysterectomy. Surgical removal of the uterus compromises the quality of life in young women. Accordingly methotrexate has been used in selected patients and has been found to be highly effective in providing a nonsurgical approach to eradicating invasive and metastatic moles. Subsequent fertility and normal pregnancy in such patients have not been impaired (104).

ALL in Children

The sequential studies leading to the development of curative treatment for ALL deserve attention, since many of the studies relating to experimental design, criteria for response, the importance of preclinical modeling, cytokinetics, pharmacology, and particularly the importance of dose, schedule, and combination chemotherapy were major targets of quantitative and often original studies in this disease (57).

Chemotherapeutic Agents

The folic acid antagonists were introduced in 1947; the glucocorticoids and adrenocorticotropic hormone in 1951; 6-mercaptopurine in 1953; vincristine and cyclophosphamide in 1961; and, more recently, asparaginase, anthracyclines, and 1-β-o-arabinofuranosylcytosine.

In 1955, a quantitative, prospective (scientific) clinical trial was first applied to cancer (66), specifically to acute lymphocytic leukemia in children, with emphasis on precisely defining the following in advance: the therapeutic hypothesis; selection of patients; treatment strategy and tactics; quantitative criteria for response; and major biostatistical input concerning experimental design, including, where appropriate, randomization and stratification, quality control, and mechanisms for data collection and analysis (66, 196).

Complete Remission

Complete remission consists of the complete clinical and hematological disappearance of disease. It was found in the above quantitative study that the most powerful discriminant for prognosis in terms of survival was the attainment of complete remission (66, 71).

Increasing the Complete Remission Rate

Given the importance of complete remission, emphasis was given to increasing the complete remission rate. This was most readily achieved with combination chemotherapy. Single agents produced complete remission rates varying from 20 to 50%, whereas combinations of chemotherapeutic agents, particularly vincristine and prednisone, produced complete remission rates of 80–90% (63, 67, 167). These studies were the first to underscore the importance of combination chemotherapy.

The fundamental rationale for combination chemotherapy is tumor cell heterogeneity, indicating the need for multtargeted therapy (116). Agents with qualitatively different mechanisms of
action are, for the most part, not associated with cross-resistance. Thus combination chemotherapy reduces the risk of emergent drug-resistant tumor cells (116). In parallel studies where dose was investigated as an independent variable, the dose-response curve was steep for both tumor and host (83). Agents which had nonmyelosuppressive dose-limiting toxicity could be used in combination at full doses and hence accrued the effectiveness of the combination without compromise in dose (59). In retrospect, the ultimate rationale for combination chemotherapy is the pragmatic one, i.e., essentially all highly effective and curative chemotherapeutic regimens represent combinations. Combination chemotherapy has become a highly sophisticated basic and clinical research discipline and has been the subject of in-depth reviews (8).

Treatment during Remission

With the high complete remission rate achieved as above, survival was somewhat improved, but all patients relapsed from remission. Accordingly treatment during remission was essential. Experimentalists, particularly Skipper et al. (171), had demonstrated the first order kinetic effect of chemotherapeutic agents. Given a homogeneous population of cells, the fractional reduction of tumor cells was constant, independent of tumor burden. Hence complete remission of the tumor represented "the tip of the iceberg" in an exponential sense and substantially further treatment (treatment during remission) was required to eradicate microscopic disease (63).

The signal studies addressed to the biology of the microscopic tumor burden as defined by chemotherapy were as follows.

Prolongation of Remission. It was demonstrated that the antileukemic agent 6-mercaptopurine significantly prolonged the duration of complete remission as compared to a placebo. This established the importance of treatment during remission and also represented the first "adjuvant" study (70).

Effect of Schedule. Methotrexate was the best single agent for treatment during remission, but relapse invariably occurred. Experimental studies in transplanted leukemias indicated that the intermittent administration of methotrexate was superior to daily administration of methotrexate (83). A study comparing twice weekly methotrexate with daily methotrexate in ALL in complete remission indicated a marked prolongation of remission with the former program (167). This established the premise that schedule could influence the therapeutic index and started the trend towards intermittent treatment. While the rationale for this approach was obscure at the time, it probably relates to the recently demonstrated evidence that in vitro drug resistance to methotrexate occurs much more readily with continuous treatment as compared to intermittent selection pressure (168).

Dose. In a randomized comparative study, it was found that a 2-fold difference in dose of agents used during remission resulted in a significant improvement of duration of remission for the higher dose (142).

Combinations. As with remission induction, combinations of chemotherapeutic agents, including, in particular, intermittent methotrexate and continuous 6-mercaptopurine administration, significantly prolonged the duration of remission as compared to single agents (64, 103).

Meningeal Leukemia

With the above high rate of complete remission and increasing duration of remissions, there occurred an increasing frequency of meningeal leukemia in patients in complete remission to the point where >50% of patients relapsed with meningeal leukemia (49). Detailed clinical studies, as well as studies of an experimental model, indicated that the central nervous system was involved with microscopic disease in the majority of patients at the time of diagnosis (78). Pharmacological studies indicated that the antileukemic agents used systemically did not pass the blood-brain barrier (146). Thus the central nervous system was a pharmacological sanctuary wherein leukemia could progress in patients in otherwise complete systemic remission.

Brain irradiation and intrathecally administered methotrexate had definite, albeit limited, effectiveness in patients with overt meningeal leukemia. It was therefore applied in quantitative studies immediately following remission induction in an effort to eradicate microscopic disease (so-called CNS prophylaxis). This resulted in a reduction of meningeal leukemia from in excess of 50% of patients in complete remission to <10% in most and <5% in some studies (3, 4, 67, 141).

The VAMP Program

A number of experimental studies indicated, and clinical studies implied, that optimal treatment would consist of maximal, intensive, intermittent "up front" combination chemotherapy. This led to the development of the VAMP program, which produced a high complete remission rate and long durations of remission but was limited by the absence of CNS prophylaxis (63, 73, 91). Nevertheless, the VAMP program served as a stimulus and prototype for subsequent combination chemotherapy studies, such as those in the lymphomas.

The Cure of ALL

The integration of the aforementioned strategies, i.e., combination chemotherapy for complete remission induction; followed by CNS prophylaxis; followed by combination systemic treatment during remission, resulted in a long-term disease-free survival (cure rate) in 40–50% of patients (102, 103, 141, 160).

The Last 10 Years. The addition of asparaginase and/or an anthracycline to vincristine and prednisone for remission induction produces complete remission rates approaching 100% and further prolongs the duration of remission (102, 141, 160).

The use of asparaginase i.m. weekly and Adriamycin during the first 6 months of remission, on a background of 6-mercaptopurine and intermittent methotrexate administration, adapted to prognostic factors has resulted in disease-free survival for standard-risk patients approaching 100% and 70% for poor-risk patients, with an overall survival of 85% (161).

Intensive multiple combination "up front" therapy, involving the intensive use of multiple agents (vincristine, prednisone, daunorubicin, Adriamycin, asparaginase, dexamethasone, cyclophosphamide, and ara-C) during the first 8 weeks of therapy, has also provided disease-free survival curves in the range of 70–80% (95).

CNS prophylaxis with radiotherapy has been associated with mild (about 10%) deficits in mentation, attention span, and other
aspects of central nervous system function (78, 133, 157). This has led to investigation of alternative approaches to CNS prophylaxis. High-dose methotrexate with leucovorin rescue supplies therapeutic levels of methotrexate to the cerebrospinal fluid, providing effective prophylaxis of CNS leukemia, particularly in standard-risk patients. The issue as to its relative effectiveness compared to brain irradiation with intralumbar intrathecally administered methotrexate is to some extent determined by risk factors (56, 143, 157).

Prognostic Factors and Tumor Biology. Prognostic factors such as age, pretreatment white blood cell count, and mediastinal mass have provided for the stratification of patients into high- and low-risk groups.

These interrelated prognostic factors have been variably powerful, depending upon the treatment. More recently, a more fundamental pathobiological classification has been made possible by immunological phenotyping. These findings are consistent with the thesis that T-cell leukemias, and probably also the B-cell leukemias, represent monoclonal expansion of a given differentiation step. Cytogenetic studies are consistent with the clonal origin of leukemia and show reciprocal translocations that may affect the activity of oncogenes. Molecular biological studies of immunoglobulin gene rearrangement indicate monoclonal arrest in patients with B-cell disease. Such changes demonstrate the B-cell origin, even of tumors that lack surface B-cell immunological phenotypes (113, 134, 149). Almost all patients can now be categorized by cell lineage and differentiation levels. Various categories may demonstrate major differences in response to treatment and prognosis.

Acute Lymphocytic Leukemia in Adults

Acute lymphocytic leukemia in adults resembles high-risk ALL in children in terms of clinical behavior, immunological phenotyping, and cytogenetics. The application of the aforementioned principles for ALL in children to ALL in adults include, in particular, the use of an anthracycline and/or asparaginase with vincristine and prednisone to achieve a high complete remission induction rate and the use of combination chemotherapy during remission. This includes alternation between cell cycle-nonspecific and cell cycle-specific agents; the use of an anthracycline early in remission; and related approaches. Disease-free survival plateaus have been achieved in 40–60% of patients, a range approaching that of high-risk ALL in children. This is particularly true of the younger adult patients who tend to have more favorable prognostic factors (7, 107, 125, 165).

Disseminated Hodgkin’s Disease

Alkylating agents were found to be effective in producing tumor regression in Hodgkin’s disease in World War II. Methotrexate and vinblastine were observed to be effective by the early 1960s, and vincristine and prednisone were separately found to be effective and, importantly, nonmyelosuppressive.

In comparative studies, Vinca alkaloid and alkylating agents were found individually to produce partial responses in 50% and complete responses in 10% of patients. Responses were slow in developing and relatively brief (2–4 months) (23).

Dose. This first randomized trial wherein dose was an independent variable was conducted in Hodgkin’s disease and non-Hodgkin’s lymphoma patients using alkylating agents and methotrexate (16, 69). Full doses of these agents produced response in 60% of the patients, whereas the random sample of patients who received one-half of the full dose had marginal antitumor effects. A similar steep dose-response relationship held for systemic toxicity.

MOMP. Given the aforementioned and the ALL experience, the four-drug combination chemotherapy study (MOMP) was initiated in 1963 (37, 62, 197). It was based on the rationale that: (a) the agents had different mechanisms of action and presumably were not cross-resistant; (b) two of the agents were nonmyelosuppressive and thus dose modifications for the combination should be minimal; (c) cytokinetic modeling and experimental in vivo studies of first order kinetic effect of single agents, drug resistance, and combination chemotherapy suggested that agents with the aforementioned activity in combination might be capable of achieving a 10–12-log cell kill, which might be sufficient to eradicate the Hodgkin’s disease (59, 63, 72); and (d) the drugs were given in combination in 10–14-day courses every 4 weeks based on experimental and clinical evidence that myeloid and immunological recovery occurred during that interval. Such intermittent treatment tended to be superior to continuous treatment not only for methotrexate but also for alkylating agents, and this effect perhaps can be generalized in experimental systems (97).

MOPP. In 1964, procarbazine, a nonclassical alkylating agent which had proved effective for the treatment of Hodgkin’s disease in Europe and in preliminary studies in the United States, was substituted for methotrexate (resulting in MOPP). Both the MOMP and the MOPP programs produced complete remission in 60–80% of the patients. These remissions, in contrast to the use of single agents, occurred rapidly and, most importantly, they were durable with an overall cure rate with very adequate follow-up of 40–50% (38, 39).

Clinical trials indicated that maintenance treatment with MOPP did not increase the cure rate, but that the duration of treatment with MOPP could be operationally determined by the rapidity with which complete remission occurred and the results of intensive (including pathological) staging prior to treatment cessation (191).

ABVD. Subsequent to the mid-1960s, additional agents were found to be active in patients with Hodgkin’s disease, including dacarbazine, Adriamycin, and bleomycin. Accordingly, Adriamycin-based combinations, such as ABVD, were developed. These combinations produced variable complete remission rates in patients refractory to MOPP in the United States, but in large quantitative studies in Italy they produced response and cure rates comparable to those achieved with MOPP (15). In a comparative study, MOPP alternated with ABVD produced a 75% disease-free survival estimate, compared to 50% for MOPP only (15). Noncontrolled studies of the MOPP-ABVD regimen with or without radiation to pretreatment sites of bulk disease have produced similar cure rates (15, 173).

Studies of treatment failure in patients achieving complete remission with MOPP indicated a remarkable pattern of relapse. As might be predicted from cytokinetic analyses, relapses occurred quite reproducibly at pretreatment sites of bulk disease. This might have major implications for treatment, particularly with respect to follow-up radiotherapy (68, 192).

Late Effects. In addition to the acute toxic effects that are well known to cancer chemotherapy, the Hodgkin’s chemotherapy...
therapy experience produced two chronic effects worthy of note. Acute myelogenous leukemia occurred with a latent period of at least 2 years following MOPP treatment in 5% of patients. On the basis of experimental studies, including mutagenicity and in vivo studies, it is concluded that procarbazine in particular, and alkylating agents as well, are the major contributors to this leukemogenesis. Of note is the fact that ABVD and programs for ALL do not use procarbazine or alkylating agents do not show an increase in secondary acute myelogenous leukemia. With a relatively large number of active agents for Hodgkin's disease, it should be possible to structure treatment programs with high cure rates which factor out agents known to be potent mutagens and carcinogens (21, 35).

The above figures for complete response and cure rates (60–80%) for Hodgkin's disease relate to patients with advanced disease, i.e., Stages III B and IV. A number of clinical trials indicate that combination chemotherapy plus limited-field radiotherapy is highly effective for patients with Stages I and II A disease and that combinations of chemotherapeutic regimens with radiotherapy may improve disease-free survival in certain intermediate stages of Hodgkin's disease (154). The interpretation of these studies, however, has been complicated by improvement in salvage therapy. Thus total nodal radiotherapy plus MOPP is superior to MOPP alone in certain studies of intermediate-stage Hodgkin's disease in terms of the initial disease-free survival, but the difference disappears with long-term follow-up because salvage therapy with radiotherapy and ABVD is superior in patients who have received one rather than two modalities as initial treatment (154).

Non-Hodgkin's Lymphoma

Shortly after the demonstration that combination chemotherapy could produce high initial complete response rates in Hodgkin's disease, the MOPP program, with cyclophosphamide as the alkylating agent (C-MOPP), was used in the treatment of non-Hodgkin's lymphoma. In diffuse histiocytic lymphoma, a 40–50% complete response rate was achieved. Essentially all of these patients remained in remission, with a cure rate of approximately 40% (36). This reaffirmation of the importance of an initial complete remission led to a sequence of studies of combination chemotherapy designed to (a) increase the complete remission rate and (b) improve the durability of complete remissions.

Adriamycin had major single agent activity in non-Hodgkin's lymphoma, including particularly DHL; the CHOP regimen, which includes Adriamycin, produced response rates of 60% and long-term disease-free survivals in the range of 30–40% (110, 128).

Subsequent studies resulted in further modifications of combination chemotherapy designed to: (a) add effective agents without compromising the dose rate of the basic CHOP components (e.g., bleomycin, high-dose methotrexate with rescue); (b) control the proliferative thrust between courses of chemotherapy for this aggressive tumor (distribute the administration of vincristine and high- or intermediate-dose methotrexate with rescue to the interface between combination chemotherapy courses); (c) add other agents of known effectiveness but which might compromise the dose of cyclophosphamide and Adriamycin (VP16, procarbazine); and (d) cycle combinations of chemotherapeutic agents (MOPACE-MOPP), with a rationale comparable to that of MOPP-ABVD for Hodgkin's disease. Perhaps the two most novel recent contributions to the combination chemotherapy of DHL were: (a) cytokinetically based adjustments in the duration of courses of treatment in the PROMACE-MOPP program; and (b) the demonstration that high-dose methotrexate with leucovorin rescue maintained the full antitumor activity of methotrexate but (with appropriate pharmacological monitoring) resulted in much reduced toxicity, thus making it ideal for combined therapy (40, 55, 61, 169, 175). Other combinations, such as COMLA (ara-C, vincristine, methotrexate with rescue, and cyclophosphamide) also produced good results. It is difficult to compare these programs across institutions, but at least four of them, (PROMACE-MOPP, M-BACOP, COP-BLAM, CHOP ± bleomycin ± VP16) produce initial complete remission rates approaching 80% and long-term disease-free survival plateaus of 50–60% (18, 55, 115, 169).

Non-Hodgkin’s lymphoma is an extraordinary heterogeneous group of diseases; it has been the subject of a sequence of hematopathologic classifications, of which the Rappoport has been the most durable and the working formulation the most recent. Pathologically the intermediate or large cell group with a diffuse pattern is cytokinetically the most aggressive and also the most subject to curative treatment with chemotherapy. However, while the cure rate for DHL is in the range of 50%, it is substantially lower for the less common forms such as diffuse poorly differentiated lymphoma and diffuse mixed cell lymphoma. Approximately one-half of non-Hodgkin's lymphomas comprise the nodular, indolent category. While these respond initially to single agent or combination chemotherapy with good remission rates and reasonable durability, the force of relapse and failure is constant over time. With the possible exception of nodular mixed lymphoma, there is no evidence that present chemotherapy is curative.

Burkitt's Lymphoma

Whether epidemic in Africa or endemic in the United States, Burkitt's lymphoma is curable by chemotherapy. Burkitt demonstrated that single-agent cyclophosphamide was curative for patients with Stage I and II disease. Relatively high cure rates have been achieved with combination chemotherapy for Stage I and II disease, with lower but definite cure rates for Stage III disease (17, 195).

Similarly lymphoblastic lymphoma, which is a T-cell disease occurring primarily in adolescents and young adults, has cure rates in the range of 40–70%, with treatment based on programs similar to those for high-risk acute lymphocytic leukemia and/or diffuse histiocytic lymphoma (184).

Acute Myelogenous Leukemia

Supportive Care. The dose-response curve for most chemotherapeutic agents is steep, and myelosuppression is the most common form of dose-limiting toxicity. Therefore the development of blood product support and antibiotics for the control of thrombocytopenia and for the prevention and treatment of infection has had a major impact on the effectiveness of chemotherapy in terms of safety and therefore in terms of dosing, with respect to both unit dose and interval between treatments. Bone marrow transplantation may be viewed, in part, as the ultimate in bone marrow support. Much of the research in blood product support and marrow transplantation began with and had its...
major impact on AML (reviewed in Ref. 88).

Remission induction. ara-C was the first agent with substantial activity in AML. When given daily, complete response rates in the range of 10–15% were achieved (47). Skipper et al. (172) in a series of elegant experimental studies in mouse L1210 leukemia demonstrated a marked influence of schedule on the therapeutic index, probably related to the cytokinetics of the tumor as compared to the bone marrow. In summary, they found that courses of ara-C which lasted twice the generation time of the leukemic cells provided substantial cytoreduction and such courses could be repeated without compromise every 4 days, an interval sufficient to allow for complete recovery from myelosuppression in the mouse. Comparative cytokinetics of AML and the normal marrow in humans indicated that the appropriate extrapolation would be 5-day courses of continuous infusion, with a 9–10-day interval between such courses (139, 172). In comparative and noncomparative studies, it was found that such intermittent treatment produced significantly higher complete remission rates (35–40%), as compared to daily treatments (15%) and significantly prolonged the duration of remission (10).

The activity of the anthracyclines was demonstrated (181). Daunorubicin is probably superior to Adriamycin because of somewhat lesser side effects relating to the gastrointestinal tract (190). When daunorubicin was combined with 5-day courses of ara-C, remission rates of 50% were achieved. Based on cytokinetic considerations, 7-day infusions of ara-C were studied, and it was found that 7 days of continuous infusion of ara-C plus three daily injections of daunorubicin (the 7 & 3 program) produced complete remission rates of 70% (145). Substantial complete remission rates were achieved in patients over 50 years of age. As with ALL 15 years earlier, the stage was set for approaches involving treatment during remission designed to prolong the duration of remission and ultimately to eradicate the microscopic tumor burden.

Early Intensification. The rationale for early intensification was based on the fact that the potential for cytoeradication was maximal immediately after complete remission induction when a microscopic, minimally drug-exposed tumor burden existed, and before the ravages of clonal evolution developed, particularly specific or pleiotropic drug resistance (96, 121).

Single, highly intensive courses of ara-C given during remission induction were attended not only by a high complete remission rate but also by a prolonged duration of unmaintained remissions (22, 25, 52, 179, 187, 188). ara-C exhibited a steep concentration viability curve against AML cells in culture (127). Such was also true in in vivo experimental animal studies. Moreover because of the cell cycle specificity and the presumed lack of stem cell effect of ara-C, bone marrow recovery tended to occur quickly (within 3 weeks) and increasing doses, which increased the magnitude of myelosuppression, did not increase the duration of myelosuppression (158, 183, 188).

Late Intensification. The rationale for late intensification with combination chemotherapy 6–12 months after treatment during remission related to the expectation that a minimal tumor burden might exist at this time and thus provide maximal opportunity for cytoeradication (11). In addition, there is evidence for delayed cytokinetic recovery of tumor cells following treatment. Such cytokinetically active cells should be more susceptible to chemotherapy (137).

In addition to the two primary agents, agents with limited but definite effectiveness have been identified; these include 6-mercaptopurine or thioguanine, azacytidine, probably vincristine and prednisone and, more recently, amsacrine and mitoxantrone. Accordingly combinations of agents which were rotated at appropriate intervals to minimize the emergence of drug-resistant lines were used (183).

Based on the above, several studies emphasizing high doses of ara-C for remission induction and/or early intensification and often including the sequencing of other active agents were undertaken during remission. These trials, in younger patients, produced complete remissions approaching 80% with continuous, complete remission curves (long-term disease-free survival) as high as 50% in pediatric AML patients (22, 183). In adults, late relapses still occur, but survival plateaus in the range of 20% have been achieved in a number of studies (28, 111, 126, 144, 182).

AML Prognostic Factor Analysis. Using multistep regression analysis over a series of studies, prognostic factor profiles for complete remission induction and for duration of remission measured from different time points were identified (76). Of considerable interest was the fact that prognostic profiles for complete remission induction differed substantially from those for duration of remission (112). With such information, patients could be segregated with respect to treatment regimens; i.e., patients with the expectation of poor response to conventional treatment could be started on new treatment. Perhaps the most compelling has been the correlation of cytogenetic abnormalities with prognosis. For example, inversion in chromosome 16 in AML is associated with an improved survival (median survival time, 25 months). Trisomy 8 has an intermediate prognosis (median survival time, 10 months), but complex chromosomal changes indicative of two or more stem lines and therefore clonal evolution and heterogeneity have a markedly adverse effect on prognosis (median survival time, 2.5 months) (194).

AML Biochemical Pharmacology. Detailed studies of the biochemical pharmacology of ara-C in patients with AML have provided significant variations which may predict prognosis on the one hand and influence the choice, dose, and duration of ara-C on the other hand. These include studies of ara-C triphosphate pool concentrations and half-times, DNA polymerase inhibition, and ara-C incorporation into DNA (114, 159, 106).

In the latter studies, it was observed that ara-C at high concentrations produced chain termination of DNA synthesis, precluding recovery of DNA synthesis, and therefore causing major cytotoxicity. At low concentrations in the HL-60 cell line, chain elongation was slowed, and differentiation of this human acute promyelocytic leukemia line in vitro was demonstrated. This was confirmed by morphological and myeloid antigen studies and was associated with a marked decrease in expression of the myc gene. Thus clinical trials designed to induce maturation have been undertaken (186).

Very high doses of ara-C have, in preliminary studies, produced substantial remission rates in patients with refractory AML and lymphoma (22).

Testicular Cancer

In the 1950s, it was demonstrated that actinomycin D produced a significant response rate in patients with disseminated nonseminomatous testicular cancer. Combinations of actinomycin-
cin D, methotrexate, and chlorambucil were equally and possibly more effective than was actinomycin D alone, and some 5–10% of patients thus treated had long-term complete remissions consistent with cure (120).

In the mid-1960s, vinblastine was found to produce partial responses in a substantial proportion of patients. It was demonstrated that higher doses of vinblastine, particularly when given in combination with bleomycin, produced significant complete response rates, some of which were durable (163).

In preclinical toxicological studies, cisplatin was demonstrated to be selectively toxic to the male gonad. Clinical trials indicated substantial activity against refractory testicular cancer (100). The stage was set for multidrug therapy.

As with all of the aforementioned studies, major attention to clinical pharmacology, toxicity, dose scheduling, and duration of treatment was essential before the optimal program, VBP, was identified. These drugs have differing dose-limiting toxicity and thus can be used in combination at full dose. It has now been widely confirmed that this combination produces a high initial complete remission rate and durable remissions in 50–70% of patients in most studies and in upwards of 90% of patients in some studies (45, 46, 75, 180). Cure is generally achieved after four courses of VBP. Patients either show evidence of refractory disease by that time or more commonly are free of clinical and marker evidence of disease and do not relapse. Testicular cancer is an aggressive disease such that relapse of patients in complete remission after cessation of treatment usually occurs within the first year, and it almost always occurs by 24 months.

Partial responses to VBP can be converted in many instances to complete responses by surgical extirpation of regressed but persisting lesions. The durability of such remissions approaches that of de novo complete remissions (41). This important treatment strategy is consistent with other evidence that high-risk sites of relapse (pretreatment sites of bulk disease and incompletely regressed lesions) after chemotherapy may be definitively controlled by surgery and/or radiotherapy.

This highly effective and curative combination chemotherapy for advanced testicular cancer raises the question as to its utility as adjuvant therapy. Patients with Stage I disease have a 10% risk, and those with Stage II disease have a 50% risk for relapse after local therapy. It was found in both comparative and non-comparative studies that two courses of VLB following local treatment produced essentially a 100% cure rate for Stage I and II disease. In order not to treat patients who do not require treatment, a sample of patients with locally controlled Stage I and II disease was followed closely, particularly by the use of tumor markers and chest film. Early relapse was identified. The cure rates for such patients with four courses of VLB approach 100%. Thus adjuvant chemotherapy is probably not required, except in high-risk patients or in patients where compliance is suspect (45).

The development of radioimmunoassays for measuring nanogram quantities of human chorionic gonadotropin and other testis tumor markers has been of critical importance in the evaluation and particularly in the tactics of treating and following patients with testicular cancer.

Major advances have been achieved in the control of central nausea and vomiting induced by chemotherapy. This is a major problem with respect to cisplatin and often precluded the delivery of adequate doses. The development of new and increasingly effective antiemetics for the control of cisplatin-induced emesis was an important step in the evolution towards curative chemotherapy for testicular cancer.

The above figures apply to patients with classical, nonseminomatous testicular cancer. Patients with extremely high hormone titers and tumor burdens and patients with extragonadal germ cell primary tumors do not respond as well, and different treatment strategies are indicated.

**ADJUVANT CHEMOTHERAPY**

The above studies and results relate to the use of chemotherapy against established clinically evident disseminated disease. Evidence in experimental in vivo tumors indicates that a given chemotherapy which is marginally effective against macroscopic, clinically overt disease may be highly effective and indeed curative against a microscopic burden of the same tumor (82, 170). Essentially all studies relating to the science of tumor biology, including cytokinetics, heterogeneity, and tumor neovascularization, strongly support the thesis that the potential for cytoreductive chemotherapy should be far greater against the microscopic (<10⁹) tumor burden as compared to clinically evident (>10¹¹) tumor burden in humans (80, 96). There are many clinical circumstances wherein the nature and the extent of the primary tumor are such that a high probability exists that disseminated micrometastases are present at the time when local control is achieved with surgery and/or radiotherapy. In such circumstances where chemotherapy has proven of moderate but limited benefit in clinically overt metastatic disease, such treatment has been moved "up front" immediately behind local control in an effort to eradicate micrometastatic disease. This is called adjuvant chemotherapy, i.e., adjuvant to local treatment with surgery and/or radiotherapy. Historically the first studies of adjuvant chemotherapy and, indeed, many of the principles of adjuvant chemotherapy were initially applied, developed, and subjected to quantitative clinical trials in the pediatric solid tumors.

**Pediatric Solid Tumors**

This heterogeneous group of relatively rare tumors includes Wilms' tumor, embryonal rhabdomyosarcoma, and Ewing's sarcoma. These tumors have been the subject of a common multidisciplinary definitive treatment strategy. Actinomycin D added to localized treatment of Wilms' tumor with surgery and/or radiotherapy increases the cure rate from 40 to 80% and was the first demonstration of the effectiveness of adjuvant chemotherapy (50). It is in these tumors that neoadjuvant chemotherapy; i.e., chemotherapy used initially to reduce local disease, was first shown to be effective in increasing the subsequent curability of radiation and/or surgery (33). For Wilms' tumor, actinomycin D and vincristine are the most effective combination; for embryonal rhabdomyosarcoma and Ewing's tumor, vincristine, actinomycin D, and cyclophosphamide, with or without Adriamycin, are the most effective (26, 89).

In a series of comparative studies, it has been established that: (a) localized treatment, including surgery and/or radiation, may be used initially if local control can be achieved; (b) chemotherapy, as above, should be applied initially if stage reduction is required for local control by surgery and/or radiotherapy; and
CURATIVE CANCER CHEMOTHERAPY

(c) chemotherapy following surgery and/or radiotherapy is required in the majority of patients to eradicate microscopic and, in some instances, macroscopic metastases. As a generalization for these tumors, radiation and surgery would be expected to cure some 30%; and with multimodality therapy, including chemotherapy, the figures approach 80% (26). Neuroblastoma is less responsive, although recent evidence with combined modality therapy featuring alkylating agents indicates that durable complete remissions can be achieved, particularly in Stage III patients (150).

Breast Cancer

Breast cancer is the most common cause of death from cancer in women. The risk of ultimate treatment failure and death in patients with breast cancer (and in other neoplastic diseases as well) can be determined by evaluating the extent of the disease following diagnosis (staging). The principal prognostic discriminant for patients with localized disease is axillary lymph node involvement. Thus local treatment with surgery and/or radiotherapy provides a 75% 10-year survival for node-negative patients. For node-positive patients, the respective figures are 15–35% (54, 93).

The lack of a disease-free survival plateau and therefore an operational definition of cure for breast cancer has been presented. Thus, the risk for failure after treatment of primary breast cancer, while it decreases with time, continues beyond 5 and even 10 and 15 years. Nevertheless some of the randomized trials of adjuvant chemotherapy for breast cancer show significant differences in favor of chemotherapy in long-term disease-free and overall survival (up to 10 years) (12, 14, 53, 92).

Axillary node-positive breast cancer patients are at high risk of having disseminated micrometastatic disease, as evidenced by the fact that usually within 1 to 3 years, but often later, the majority (70–90%) of patients who will relapse do so with clinically overt disease. Clinically overt metastatic disease can be treated effectively with chemotherapy or hormonal therapy, but treatment failure eventually occurs and the patient is destined to die of the disease.

There are a number of chemotherapeutic agents, including alkylating agents, antimitabolites such as methotrexate and fluorouracil, and Adriamycin, which individually produce response rates in 25–50% of patients. Combinations of chemotherapeutic agents in comparative and noncomparative studies produce higher response rates (in the range of 50%), with combinations involving Adriamycin being perhaps superior; i.e., they produce response rates in the range of 60–70% (93). This degree of responsiveness of clinically overt disease (high tumor burden disease) would suggest that such treatment applied to low tumor burden disease (micrometastases immediately following control of the primary tumor in patients with Stage II disease, adjuvant chemotherapy) might be capable of eradicating the tumor. In experimental transplanted tumors, there is definitive and widely confirmed evidence that a chemotherapy program which is only partially effective against a high tumor burden has a much higher probability of being curative against a low tumor burden (61, 82, 170). Moreover the effectiveness, in terms of producing tumor regression in the high tumor burden setting, correlates with curability for the same treatment in the low tumor burden setting. As a result of the above, adjuvant chemotherapy for patients with node-positive breast cancer in studies using modern tumor biological, chemotherapeutic, pharmacological, and experimental design concepts and techniques was begun in the early 1970s. These early studies, where chemotherapy was compared to no treatment, indicate that, particularly for premenopausal women, disease-free survival is significantly improved as a result of adjuvant chemotherapy (12, 14, 53, 92). Combination chemotherapy, usually CMF or close analogues thereof, is superior to single-agent therapy (31, 93). The initial concept of maintenance treatment carried out for 2 years is probably inappropriate, inasmuch as there is experimental (Skipper) and now clinical evidence that more short-term treatment is equally effective. Thus where duration of treatment was an independent variable, CMF for 6 months proved as effective as CMF for 12 months (176), and a combination of Adriamycin and cyclophosphamide for 4 months was as effective as the same regimen delivered over an 8-month period (94).

Retrospective analysis of clinical studies (13), as well as numerous experimental studies, suggest that dose, or more properly dose rate, correlates with the capacity of the treatment regimen to control micrometastatic disease; however, some other clinical studies have not confirmed this. Thus high priority must be given to prospective studies where dose is the independent variable. Hormone therapy, when added to chemotherapy, in postmenopausal, estrogen receptor-positive women, in relatively short-term studies, further improved disease-free survival (52). Whether combinations including Adriamycin are superior to those without and whether relatively recently introduced strategies, such as the rotation of non-cross-resistant combinations, will improve effectiveness remain to be determined.

The most important, but also the most difficult, question is whether adjuvant chemotherapy has significantly increased the cure rate. Two of the best designed studies, which also have the longest follow-up (10 years), are the melphalan versus control (NSABP) (53) and the CMF versus control (Milan) (14) studies. Here disease-free survival, particularly in premenopausal patients, is clearly superior in patients receiving chemotherapy. More important, overall survival is significantly superior at the 11-year (maximum) follow-up point (a 20% improvement) for premenopausal patients. This improvement in survival appears early and progresses with time. Two other major studies demonstrate improved disease-free and overall survival for adjuvant chemotherapy in both pre- and postmenopausal patients with 8- and 15-year follow-up (79, 136). Several reports, however, do not confirm the effectiveness of adjuvant chemotherapy in postmenopausal patients.

Small Cell Lung Cancer

This cytokinetically aggressive tumor is responsive to a variety of chemotherapeutic agents. For patients with clinically limited disease (i.e., disease limited to the chest), complete response rates of 40–60% can be achieved with combination chemotherapy (29, 123).

Relapse in the central nervous system is common, occurring in 25% or more of patients. This can be reduced to <5% by cranial irradiation early in complete remission (123). A more common site of relapse in patients entering complete remission is at the pretreatment site of bulk disease in the chest. Irradiation here will also reduce the risk of local, thoracic relapse from 60%
to as low as 15–25% (105). Remission induction with combination chemotherapy and particularly the rotation of combinations of chemotherapeutic agents during remission for up to 1 year have markedly improved disease-free and overall survival for this disease (29, 124). While the majority of patients relapse, some 10–20% of patients with limited, small cell lung cancer will continue disease free beyond 3 or 4 years (29, 123, 124). While the risk of relapse markedly decreases after 2 years, 19 of 97 patients disease free at 2.5 years subsequently relapsed, 2 after 8 years (6).

**Osteogenic Sarcoma**

Local control can almost always be achieved for this tumor by amputation. Nevertheless the survival rate for the 30 years preceding the 1970s was in the range of 20% largely because of the development of lung metastases (74, 129).

In the early 1970s, it was demonstrated that high-dose methotrexate with rescue produced responses in a small proportion of patients with advanced disease and, when used as adjuvant chemotherapy immediately following surgery, produced a disease-free survival plateau of 40% (108). At about the same time, Adriamycin was found to be comparably effective (32). The combination of high-dose methotrexate and Adriamycin in the adjuvant setting, particularly where dose rate of the individual agents was preserved, produced the expected additive rate, i.e., disease-free survival plateaus between 50 and 60% (84). These agents in various combinations with cisplatin and other agents in a variety of studies produce disease-free survival plateaus in the range of 50–70% (24), and in a more complex combination, but featuring, in particular, high-dose methotrexate and Adriamycin, a disease-free survival plateau of 70–80% has been achieved (151, 185).

In the mid-1970s, stimulated by the capacity of chemotherapy to produce tumor regression, limb-preserving surgery was developed. Chemotherapy before surgery, i.e., neoadjuvant chemotherapy, often resulted in cytoreduction in the primary tumor, providing an improved opportunity for local bone tumor resection and endoprosthesis insertion (43, 109, 152).

In addition, preoperative chemotherapy provides an opportunity to evaluate the effectiveness of high-dose methotrexate with or without Adriamycin against overt disease and to correlate this with subsequent survival which is a function of the capacity of chemotherapy to control micrometastatic disease. It was found that cytoreduction by chemotherapy of the primary tumor was correlated with eradication of micrometastatic disease, mainly in the lungs, when the same chemotherapy was continued after control of the primary tumor. Accordingly response of the primary tumor was used as a measure of effectiveness of chemotherapy, and major adjustments were made in the adjuvant program for patients in whom primary tumor regression was suboptimal (151, 185).

Osteogenic sarcoma is a rare disease, such that comparative studies are difficult, if not impossible, to conduct in single institutions. Clinicians at the Mayo Clinic noted a progressive increase in disease-free survival of osteogenic sarcoma into the early 1970s in the absence of adjuvant chemotherapy. Therefore, they conducted a study in the mid-1970s, wherein patients, following control of the primary tumor, were randomly allocated to high-dose methotrexate with leucovorin rescue or to an untreated control group (42). In a relatively small sample of patients (only 30% of eligible patients agreed to randomization), there was no difference between the two groups, both having disease-free survival plateaus in the range of 40% (42).

Does adjuvant chemotherapy indeed improve the cure rate of patients with osteogenic sarcoma, or have we been a victim of the vagaries of early diagnosis, evaluation, and other factors which might change the natural history? To answer this question, two randomized studies were undertaken, one a single institution (UCLA) study, and the other in a cooperative group (POG). Following surgical control of the primary tumor, patients were randomly allocated to combination chemotherapy, featuring high-dose methotrexate with rescue and Adriamycin, or were allocated to no-treatment control groups. These studies have been completed, and a highly significant difference in 2-year disease-free survival in favor of the chemotherapy arm was observed in both studies (44, 122).

**Soft-Tissue Sarcomas in Adults**

Metastatic soft-tissue sarcoma is responsive to Adriamycin, which produces partial responses in approximately 30% of patients (138). In most studies, this is increased to 40 to 60% by the addition of dimethyltriazinoimidazolecarboxamide, cyclophosphamide, and perhaps vincristine (8, 85, 86). From 10 to 15% of such patients with overt metastatic soft-tissue sarcoma achieved complete remission, about one-third of which (3 to 4% of the total) are durable (189).

Adriamycin and Adriamycin combinations were therefore evaluated in the adjuvant treatment of high-grade soft-tissue sarcomas, where local control had been achieved. In randomized studies, both positive and negative results have been reported (2, 155). Improved overall survival for all patients in recent years, probably because of better control of the primary tumor through integrated surgery and radiotherapy, has complicated the design and interpretation of adjuvant studies (174). A large controlled intergroup study of the role of adjuvant chemotherapy in soft-tissue sarcomas is ongoing.

**Gastric and Rectal Carcinoma**

Gastrointestinal carcinoma is generally poorly responsive to chemotherapy. While response rates of up to 40% for gastric carcinoma using combination chemotherapy have been achieved, the figures for the remainder of nonsophageal gastrointestinal carcinomas are in the range of 20% (132). Nevertheless major multiinstitutional adjuvant chemotherapy trials have been undertaken.

For Stage II, a regional gastric carcinoma, a multiinstitutional study has compared fluorouracil plus methylcylohexylxinitosourea to a no-treatment control arm following surgery. There was a significant (approximately 20%) improvement in disease-free and overall survival in the adjuvant arm (30). However, negative studies have been reported (101).

In a study of high-risk localized rectal carcinoma conducted by the same multiinstitutional group (Gastrointestinal Tumor Study Group), the addition of postoperative radiotherapy increased local control as compared to a randomized control group. The addition of fluorouracil plus methylcylohexylxinitosourea produced a further and significant (20%) improvement in disease-
free and overall survival (131). These studies of gastric and rectal carcinoma await confirmation and extension.

Bone Marrow Transplantation

Bone marrow transplantation exploits the dose effect, both for radiotherapy and for chemotherapy (usually cyclophosphamide). It has been most effective when used in patients with acute leukemia in the minimal tumor burden setting that is present early in complete remission (177). A low cure rate was achieved for acute myelogenous leukemia with total body radiation only. Cyclophosphamide, when added to total body radiotherapy, increased the cure rate. In AML, some 50% of patients treated early in complete remission and supported by histocompatible bone marrow transplantation are cured (177). Thirty % die, largely of graft-versus-host disease. Only 20% have relapse of leukemia. Comparable figures have been achieved with combinations of intensive cyclophosphamide and busulfan (164). Similar programs with matched allogeneic or autologous bone marrow (with or without chemotherapy or immunological approaches to controlling bone marrow “contamination”) have provided a variable proportion of long-term disease-free survivors in patients with acute lymphocytic leukemia in second or subsequent remission (147, 177), patients with acute myelogenous leukemia (177), selected patients with chronic myelogenous leukemia in stable phase (confirmed by eradication of the Philadelphia chromosome) (51), and in patients with various types and stages of high-risk non-Hodgkin’s lymphoma (135, 140).

Ovarian Cancer

Cytoreductive surgery (debulking) improves response to subsequent chemotherapy in terms of duration of disease control (87). Thus, surgery plays a relatively novel role for Stage III and IV ovarian cancer in terms of reducing the tumor burden in preparation for systemic treatment and also is used in end staging (second look) to determine the effectiveness of systemic treatment following debulking. The alkylating agents have long been known to be effective in producing tumor regression in perhaps 50% of patients with ovarian cancer. The addition of Adriamycin and of cisplatin has increased the overall response rate and particularly has resulted in complete clinical tumor regression in 40% of patients (27, 193). Up to 50% of Stage III and IV disease patients who achieve complete clinical tumor regression will, with end staging (second look operations), be microscopically disease free. In those studies using this approach with 5-year or greater follow-up, there is evidence that 15–20% of all patients with Stage III and IV disease so treated are clinically and microscopically disease free (27, 47, 193). Whether this can be improved upon by more effective chemotherapy (34), by more effective initial surgery, by monitoring ovarian antigen, and by monitoring with second-look operations, intraperitoneal chemotherapy, and/or immunological approaches remains to be determined (27, 34, 147, 193).

NEoadjuvant CHEMOTHERAPY

The improved effectiveness of chemotherapy in squamous cell carcinoma, largely as a result of the use of platinum-based combinations, has reopened these diseases to approaches involving initial chemotherapy in an effort to reduce the size of the primary tumor (stage reduction), such that the primary tumor becomes operable and/or treatable with radiotherapy with curative intent. In addition, disseminated micrometastatic disease, the risk of which will depend on the primary site, type, and extent (stage), will also be addressed initially (58). This is of importance in view of the fact that micrometastatic disease is probably kinetically more aggressive than overt disease and thus at considerable risk of mutation to drug resistance. Mutation theory, modeling, and experimental studies suggest that the risk of micrometastatic disease developing resistant cell lines over a relatively short time period (several months) may be major (80, 168). To this extent, the initiation of systemic treatment in the form of neoadjuvant chemotherapy avoids the 1- to 2-month delay which is likely to occur if the primary tumor is treated initially with surgery and/or radiotherapy. Neoadjuvant chemotherapy with respect to childhood tumors and osteogenic sarcoma has already been discussed. The development of increasingly effective agents and combination chemotherapy for squamous cell carcinomas has suggested that the neoadjuvant approach may be an idea whose time has come.

In head and neck cancer, in which neoadjuvant chemotherapy is under the most intensive study, several combination regimens, which include cisplatin, can produce initial tumor regression rates of 70 to 90%, with complete response occurring in 20 to 50% of patients (1, 48, 77). Following chemotherapy, such patients are treated with surgery and/or radiotherapy with curative intent. Whether surgery should be decreased in terms of extent of resection and radiotherapy reduced in terms of field size and dose because of prior tumor reduction with chemotherapy response remains controversial. What seems clear in some studies is that survival after surgery and radiotherapy correlates with the degree of response to neoadjuvant chemotherapy. Thus patients who achieve complete remission after chemotheraphy have relatively high survival rates, as compared to those who achieve partial responses (1, 48). It remains to be determined whether this approach will in fact increase the cure rate in patients with advanced (Stage III and IV) head and neck cancer. Other tumors for which neoadjuvant chemotherapy is the subject of study include Stage III regional non-small cell lung cancer, Stage III breast cancer, esophageal cancer, bladder cancer, anal carcinoma, and, as above, osteogenic sarcoma.

CONCLUDING AND SUMMARY REMARKS

The final arbiter of advances in curative treatment for a given disease must be reduction in national mortality attributable to such treatment. As indicated in the introduction, it may take 5 to 20 years from the time of introduction of curative treatment to recognize its impact on national mortality. For certain diseases where there has been a major impact of curative cancer chemotherapy, where such treatment has been in effect for a substantial number of years, and where the disease is dynamic, a significant reduction in mortality has, in fact, occurred. For example, this has been conclusively demonstrated for acute lymphocytic leukemia in children, Hodgkin’s disease, diffuse histiocytic lymphoma, pediatric solid tumors, testicular cancer, and gestational trophoblastic cancer (117, 130).

A more current and therefore relevant measure of the impact of curative treatment is presented in Table 1. Even here, the time lag and some of the other problems mentioned in the introduction...
are pertinent, but they are not as restrictive as those relating to mortality. In the first column of Table 1 are listed the 11 (or 14 if pediatric solid tumors are divided into their components) tumors which can be cured by chemotherapy (see above). The incidence figures are the number of new patients diagnosed with that therapy, the rapidly emerging field of tumor immunology, and inversely related to age. Thus the diseases wherein a high cure rate is achieved are disproportionately represented in the pediatric and young adult population. Hence the overall impact on survival is substantially greater than the figures in Table 1 indicate.

With rapid advances in basic tumor biology and clinical investigation, it is probable that advances in curative treatment will continue. New strategies relating to chemotherapy and hormonal therapy, the rapidly emerging field of tumor immunology, and refinements in surgery and radiotherapy are under development. The in vitro tumor stem cell assay may allow for assessing patient responsiveness to antitumor agents and thus the individualization and optimization of treatment (162). Basic science studies relating to oncogene products, differentiation, immunotoxins, microenvironmental signals, and drug resistance, to mention a few, provide new targets, strategies, and tactics for the immediate future. Therapeutic ferment has led to the expectation by many experts that progress in the curative treatment of head and neck cancer, selected stages of lung cancer, esophageal cancer, rectal cancer, bladder cancer, anal cancer, and cervical cancer may be under way.

Long-term disease-free survival (cure) for patients with cancer is increasing. This has led to increasing emphasis on the quality of life. In contrast to some chronic diseases, the vast majority of patients cured of cancer return to full activity with little or no compromise in the quality of life. Emphasis on less radical procedures for breast cancer (90) and limb preservation procedures for extremity cancers (152, 153) are representative of such efforts. The potential long-term adverse effects of chemotherapy, such as the increased risk of leukemia, are being intensely studied, particularly with the deletion of those chemotherapeutic agents which have major mutagenic and carcinogenic activity, where this can be accomplished without significantly compromising the cure rates (20).

Thirty years ago it was widely held that cancer could not be cured by chemotherapy. Ten years ago it was conceded that tumors of hematological and embryological origin might be curable, but the more common epithelial tumors would not yield to chemotherapy. Progress has been steady and has accelerated as such dire predictions have been progressively set aside. While progress has been substantial and real, we still have a long way to go. The current revolution in basic tumor biology, continuing clinical innovations, and the interaction between the two provide realistic optimism for continuing progress in the curative treatment of cancer.

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Curative Cancer Chemotherapy

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