New Approaches in Administration of Anticancer Drugs

David P. Rall
National Cancer Institute, NIH, Bethesda, Maryland 20014

Summary

Some of the factors which seem to be important in successful chemotherapy are (a) extent of disease, (b) measurability of disease, (c) availability of an effective drug for remission induction, (d) treatment during remission, and (e) treatment related to the proliferative state of the tumor. Chemotherapy of such important tumors as carcinoma of the lung, breast, or colon is considered in relation to these factors. These considerations suggest the need for clinical studies aimed at creating successes out of failures. Treatment should be begun when there is minimal tumor present, preferably immediately after surgery. Multiple long-term chemotherapy in remission should be employed. Such studies are based on sound scientific principles and are urgently needed.

Introduction

In an attempt to identify the most fruitful pathways for future research, it is often necessary to look to the past. To look, for instance, at past successes and failures in cancer chemotherapy to determine if they might suggest approaches that could yield more successes and fewer failures.

This last decade has seen some notable successes in cancer chemotherapy and some even more notable failures. The treatment with drugs of childhood acute lymphocytic leukemia, choriocarcinoma in women, and Burkitt's lymphoma can now yield a significant number of either long-term survivors or cures. In contrast to this, the results of chemotherapy with carcinoma of the lung, colon, or breast have been bleak.

The purpose of this communication is to analyze some factors which appear to be important in the successful chemotherapy of lymphocytic leukemia in children, Burkitt's lymphoma, and choriocarcinoma in women, and to determine the applicability of these factors to the important tumors thus far resistant to chemotherapy. These factors are (a) extent of disease, (b) measurability of disease, (c) availability of a safe effective drug for remission induction, (d) treatment during remission, and (e) treatment related to the proliferative state of the tumor.

Extent of Disease

Let us first consider the influence of the body burden of tumor on the response to chemotherapy. Data from J. Ziegler and P. Carbone (personal communication) indicate that 90% of the patients with Burkitt's lymphoma who are treated with only local manifestations of the disease can be brought into long-term remission with cyclophosphamide. Similarly, it is well known that up to 95% of children with acute lymphocytic leukemia can be brought into reasonably long-term remission with chemotherapy. What are the results with similar therapy when the chemotherapy is initiated in patients who present themselves with extensive, late disease? Carbone and Ziegler have shown that instead of 90%, less than 20% of the patients with extensive, metastatic Burkitt's lymphoma will go into long-term remission. It is difficult to find studies on children with acute lymphocytic leukemia that are related to the extent of disease, but it is clear that children with extensive advanced disease, brought into the clinic late have a lower response rate than children with limited, apparently early disease. Similar information is available relating output of chorionic gonadotropin to curability of choriocarcinoma. Patients with high urinary concentrations of chorionic gonadotropin, suggesting a high body burden of tumor, have a poor prognosis (5). Goldin showed years ago that treatment of early leukemia L1210 with Methotrexate can be curative, whereas treatment with Methotrexate in late L1210 was palliative at best (3).

There are at least 3 aspects to the different response in early and in late disease. One, made elegantly clear by the studies of Skipper and his colleagues, is the log kill concept of drug action as related to the number of tumor cells present in the host. In addition to the absolute number of tumor cells, the localization of tumor cells is important. In late, extensive disease, neoplastic cells can enter into sanctuaries in which drug concentrations never reach levels adequate to eradicate the tumor. In addition to known sanctuaries within the central nervous system, other areas such as thymus and the gonads, and the poorly perfused interior of large solid tumors, may be important. The poor response of patients with advanced disease may be a function of both total number of tumor cells and the number of tumor cells localized in areas of limited drug supply.

A third factor is the possibility that, as the tumor grows large, the proliferative state of the tumor changes. A higher fraction of the tumor cells may enter a hypothetical non-proliferating pool. These cells are relatively resistant to chemotherapeutic agents, particularly antimetabolites.

This emphasizes the necessity for early diagnosis and early treatment of cancer. This statement of course is trite, but with lung, breast, and colon carcinomas, early diagnosis has generally led the patient to the surgeon and to surgical treatment. If the patient is not referred to the chemotherapist until late recurrence with extensive disease, the prospect for chemotherapy is bleak.
Measurability of Disease

A second characteristic of tumors which respond well to drugs is that of easily measurable disease. There are easily followed parameters by which the extent of the body burden of tumors can be rapidly estimated in acute lymphocytic leukemia and choriocarcinoma. Early Burkitt's lymphoma is superficial, and the size of the lesions is easily followed. It becomes important then to consider how we can measure the effect of chemotherapy on the tumor cell population of lung, breast, and colon carcinoma. One method is to follow the size of measurable tumors as has been done for many years in cancer chemotherapy. Recent studies (2) have shown that a simple decrease in tumor size may underestimate greatly the number of viable tumor cells killed. A 50% decrease in tumor volume may represent a 99+% decrease in viable tumor number. The difference represents nonviable (killed) cells which are slowly removed. Chemotherapists must be alert to this possibility when they follow patients with measurable tumors.

Another approach is to measure the survival time of the patient. And this is the essence of chemotherapy. I was fortunate enough to obtain data concerning the survival time of control and treated patients with bronchiogenic carcinoma from the Veterans Administration Lung Cancer study group chaired by Julius Wolf (personal communication).

If one is willing to make some assumptions, and these assumptions are not as critical as they seem, one can interpret survival time data from patients in a very interesting manner.

Patients were classified in the V. A. Lung Group into an extensive disease group or a limited disease group. I made the assumption that (a) the lethal tumor burden was $10^{12}$ cells (1 kg tumor), (b) the extensive disease tumor burden was $10^{11}$ cells (100 gm), and (c) the limited disease was $10^{10}$ cells (10 gm).

The survival time of patients with extensive disease was 58 days. Survival time of patients with limited disease was about 120 days. Since the time span of these studies was rather limited, I assumed that the doubling time was constant. From these data, then, the volume-doubling time of these tumors could be estimated to be about 18–17 days.

In one protocol, Methotrexate was given in five-day courses every 30 days. This group showed an increase in lifespan from 60 days to approximately 75 days. It is possible to estimate that approximately 50% of the tumor was destroyed by those three courses of Methotrexate or about 17% for each course. Slightly better results were obtained with cyclophosphamide given on the same schedule (Chart 1).

Bergsagel et al. (1) have performed similar studies using cyclophosphamide on a different schedule (Chart 2). In these studies nitrogen mustard served as a control instead of a placebo, and apparently nitrogen mustard is indistinguishable from placebo, since the median survival time was 57 days.

Cyclophosphamide was given in a single large dose every 21 days intravenously. The dose averaged 1.4 grams per square meter. The median survival was 126 days. It is possible to estimate that much tumor was destroyed; approximately 60% was destroyed after each dose. This suggests that nonproliferating cells were killed by cyclophosphamide.

This interpretation of these data demonstrates one approach to the use of survival time data to gain an understanding of the effect of therapy on the tumor. This approach might have considerable usefulness in understanding chemotherapy and suggests that this tumor is not unresponsive to chemotherapy. It is interesting to present these data in a format used by laboratory animal chemotherapists. As can be seen in Table 1, substantial increases in life span were obtained with chemotherapy. It should be noted that there are problems associated with studies utilizing survival time. If these studies are successful and lead to increasing survival times, then the duration of the study can become discouragingly long.
Availability of Remission-inducing Agents

The third characteristic of the 3 tumor situations in which we have reasonable success is the availability of a safe effective drug, a nontoxic remission inducer. For instance, for use on acute lymphocytic leukemia we have not only vincristine and cortisone, but now asparaginase. With Burkitt's lymphoma and choriocarcinoma the initial treatment can be given with safety and generally brings about an almost immediate complete or near complete remission. It is important that available drugs are either relatively nontoxic or can be given to patients in adequate doses with safety, i.e., with easily tolerable toxicity. The ability to predict the response of any one patient to any dose of a drug becomes important. One major aspect of this is the possibility of drug-drug or drug-host interactions which alter the toxicity of anticancer drugs and alter response in patients with altered physiologic states (4). The chemotherapist must be alert for examples of inadvertent combination chemotherapy.

The criteria necessary for an agent to be considered effective at inducing remissions are simple. It should reduce the tumor size 99% or better, and it should do so with predictable safety.

Using these criteria, perhaps surgery might be considered a nontoxic remission-inducing agent for the common carcinomas. In most instances surgery can reduce the tumor size between 90–99% with relatively little host damage and with rapid recovery. The remaining tumor cells might well be susceptible to chemotherapy.

Treatment in Remission

Treatment of patients with childhood acute lymphocytic leukemia and choriocarcinoma, though possibly not Burkitt's lymphoma, while they are in remission has been another important characteristic of successful chemotherapy. The obvious reasons include both a smaller tumor burden and greater host resistance to drug toxicity.

One argument against treatment in remission has been the possibility that chemotherapy may suppress those host immunologic mechanisms which may aid in the control of small amounts of residual tumor. However, in Burkitt's lymphoma, multiple treatment in remission with cyclophosphamide in early disease yields the same high percentage of long remissions as does a regimen consisting of a single dose of cyclophosphamide for induction only with no treatment in remission (Ziegler and Carbone, personal communication).

Closely related to this is consideration of multiple drug therapy. There is good evidence that drugs in combinations are more effective than drugs given singly in the treatment of acute lymphocytic leukemia. The use of combinations, concurrent and sequential, has increased the incidence of complete remissions in choriocarcinoma. The advantage of giving two drugs of differing host toxicities (that is, of independent drug action) is obvious.

Types of Drugs and Proliferative State of Tumor

The last important area that needs consideration is to relate the type of drugs used to the rate of proliferation of the tumor being treated. In such diseases as acute lymphocytic leukemia, Burkitt's disease, and choriocarcinoma, the tumor cells are proliferating at a relatively rapid rate, and there is a relatively low fraction of nonproliferating cells. In such diseases either alkylating agents (as a general class) or antimetabolites seem to be effective. With many solid tumors, of clinically observable size, a large fraction of the cellular population appears to be in a nonproliferating state. These cells are viable but not in the active mitotic cycle.

Antimetabolites such as Methotrexate, cytosine arabinoside, 6-mercaptopurine, and possibly fluorouracil are relatively ineffective against such tumors. They may be very effective in killing the 1–10% of the cells in active proliferation, but they do not affect the great majority of the tumor. Alkylating agents such as cyclophosphamide, phenylalanine mustard, and similar compounds may be able to exert some lethal effect on cells which are not in the active mitotic cycle. As an example, in the treatment of lung cancer with high intermittent doses of cyclophosphamide, about 60% of the tumor seemed to have been destroyed by each dose. Thus some combination of cell cycle specific and nonspecific agents should be used to treat large solid tumors. There are at least two alternatives. Use of a cell cycle state-specific agent might be considered if given every few days for a very long time. One might visualize that as the proliferating cells were destroyed by the agent, a new crop of cells would subsequently enter the proliferative state. Closely spaced doses of an antimetabolite type agent might then be effective. Such a schedule, however, yields considerable host toxicity. Alternatively, after a dose of an alkylating agent, there might be considerable cell damage with perhaps one or two logs of cell kill. In the two or three weeks subsequent to that, one would anticipate that the proliferative rate of the remaining cells would increase and that the

New Approaches to Drug Administration

<table>
<thead>
<tr>
<th>Drug &amp; schedule</th>
<th>Median survival time (days)</th>
<th>Total cell kill (%)</th>
<th>Increased survival time (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control or HN2</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX × 5 q 30 days</td>
<td>72</td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td>CYP × 5 q 30 days</td>
<td>82</td>
<td>63</td>
<td>41</td>
</tr>
<tr>
<td>CYP q 21 days a</td>
<td>126</td>
<td>96</td>
<td>117</td>
</tr>
</tbody>
</table>

Chemotherapy of late bronchiogenic carcinoma. MTX, Methotrexate; HN2, nitrogen mustard; CYP, cyclophosphamide.

All data are from the Lung V. A. Group (J. Wolf, personal communication), except which is from Bergsagel et al. (1).
administration of a cell cycle state specific agent might be effective on a cell population now much more susceptible to such therapy. 

More use could be made of the principles of independent joint toxicity. Agents such as vincristine and asparaginase, which have little effect on the bone marrow or gastrointestinal tract, can be added in full dose to other chemotherapeutic agents which do exert major toxic effects on these organs.

Comment

I wonder if the progress with chemotherapy in childhood leukemia, Burkitt's disease, and choriocarcinoma, and with radiotherapy in Hodgkin's disease, is due in part to the fact that these are among the neoplastic diseases in which surgery is consistently ineffective. Since surgery is useless, the patients are referred to chemotherapists. After years of effort, trials, and failures, successes in these diseases are now occurring. The patients are referred to chemotherapists early, and treatment can be initiated under the best possible circumstances.

Could chemotherapy be more effective than hormonal therapy in breast carcinoma? Could chemotherapy produce a greater cure rate in Hodgkin's disease? Hormonal manipulations and radiotherapy are now "standard therapy," and appropriate meaningful chemotherapy protocols are considered experimental and therefore dangerous. But I wonder what would have been standard therapy if chemotherapy and the increasingly rigorous and scientific protocols of the chemotherapists and the cooperative groups had been instituted 20 years ago?

Conclusions

These considerations suggest the urgent need for clinical studies aimed at creating successes out of failures. The principles that should be followed in treating the common solid tumors are: (a) Treatment should begin when there is minimal tumor. The obvious time to do this is immediately after surgery. Surgery which does not have a high probability of curing the patient could be an effective nontoxic remission-inducing agent for such patients. (b) Multiple long-term chemotherapy in remission should then be employed. Perhaps the most logical course would be alteration of cell cycle stage-specific and cell cycle stage-nonspecific agents, somewhat intensively at first, with repeated courses at intervals for a long time. Such patients should be followed for recurrence and survival. Since this type of patient should have a significant number of recurrences within 1 or 2 years, some evidence of the effectiveness of such a program could be determined within that period of time. If survival is increased in these patients, then the final results might take years to evaluate. Such studies are based on sound scientific principles and are urgently needed.

"They are ill discoverers that think there is no land when they see nothing but sea."—Bacon, the Advancement of Learning.

REFERENCES


New Approaches in Administration of Anticancer Drugs

David P. Rall


Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/29/12/2471