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Current Problems in the Use of the Oncolytic Drugs

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For the patient whose cancer is detected early and whose tumor has not yet become disseminated, surgical resection and radiation therapy offer a good possibility for cure. For the less fortunate patient whose tumor has spread too widely for surgery or radiation to be potentially curative, the physician is justified in employing oncolytic drugs. Oncolytic drugs do not help every patient and are usually not curative. However, in some cases if carefully used, they can produce tumor regression, alleviate distressing symptoms and prolong survival for significant periods of time.

Tabs. 1 and 2 list the more commonly occurring neoplastic diseases of adulthood and indicate which of the oncolytic drugs are most likely to be effective in their treatment. These tables also provide some information on the type of benefit which may result from these drugs.

Tab. 3 lists some of the more common childhood malignancies and provides information on their chemotherapeutic treatment. It should be noted that the prognosis of childhood cancer is better than that of adult cancer and that chemotherapy is potentially curative in an appreciable percentage of cases even after they have become widely disseminated.

Tab. 1. Remission and prolongation of life

Neoplasm	Drugs used	Benefit	
		% Remission	Prolonged life
Chronic Myel. Leukemia	Busulfan, 6 MP (Hydroxyurea)	90	Probable
Chronic Lymph. Leukemia	Chlorambucil	80	Definite
Hodgkin's Disease	VLB, Mustards, Methylhydrazine	80	Probable
Prostatic Ca.	Castration, Estrogens	70	Definite
Chorionic Ca.	MTX, ACT, VLB	70-80	Definite
Lymphosarcoma	Mustards, VCR, VLB, Steroid	50	Probable
Reticulum Cell Sarcoma	VCR	50	Not Definite

Tab. 2. Remission and prolongation of life

Neoplasm	Drugs used	Benefit	
		% Remission	Prolonged life
Head & Neck Squamous Ca.	VLB, MTX	50	Not Definite
Ovarian Ca.	Mustards, VLB	40	Not Definite
Testicular Ca.	ACT, VLB, Mustards	40	Probable
Myeloma	Mustards, Urethan	35	Not Definite
Endometrial Ca.	Progestagens	30	Not Definite
Breast Ca.	Castration, Androgens, Estrogens, 5FU, VLB, Progestagens	25	Probable

Tab. 3. Children's malignancies Remission and prolongation of life

Neoplasm	Drugs used	Benefit	
		% Remission	% "Cures"
Acute Leukemia	Steroids, VCR, MTX, 6MP	90	<0.2
Neuroblastoma	Mustards, VLB, ACT, VCR	40	5
Wilm's Tumor	ACT, VCR	40	2
Embryonal Rhabdomyosarcoma	ACT, VCR, Mustards	20	2

The abbreviations used in these tables are as follows:

ACT	= actinomycin D	6MP	= 6 mercaptopurine
5FU	= 5 fluorouracil	VLB	= vinblastine sulfate
MTX	= methotrexate	VCR	= vincristine sulfate

The order in which these drugs are listed next to a neoplasm indicates the order in which they are usually employed and reflects their relative effectiveness against that neoplasm. However, on occasion, the order may differ depending on a patient's bone marrow status and his ability to withstand the toxicity of a particular drug. Furthermore, tables such as these, which were made during April 1966, require constant modification to reflect the latest developments in therapeutic research.

Tab. 4 lists the neoplasms which only rarely respond to currently available oncolytic drugs and for which most cancer chemotherapists do not, therefore, employ this type of treatment. As an example of the way in which therapeutic research

Tab. 4 Chemotherapy not frequently effective

Melanoma	Stomach	Pancreas
Liver	Brain	Cervix

Sarcomas of Bone and Connective Tissues

constantly modifies opinions such as are summarized in Tab. 4, it may be mentioned that carcinoma of the cervix probably deserves to be removed from Tab. 4 to Tab. 2. In recent clinical trials at the Roswell Park Memorial Institute for Cancer Research, 6 of 9 women with carcinoma of the cervix responded significantly to treatment with vincristine sulfate (Costa *et al.*, 1962; Hreschchyshyn, 1963). Theoretically then, treatment with this drug could convert some "inoperable" patients with carcinoma of the cervix into patients who could benefit from radical surgery. This method for converting inoperable cases to an operable status has been successfully employed for some pediatric malignancies (James *et al.*, 1964).

The dosage magnitude, route, and frequency of administration of an oncolytic drug all have important influences both on the percentage of patients who respond and on the duration of their responses. From time to time, therefore, such tables as 1 through 4 require revision not only to include new drugs but also to provide information on the improved results which may be obtained by new methods of administering the "older" drugs.

When should oncolytic drug treatment be started for the patient who remains active and essentially asymptomatic but whose inoperable tumors have become disseminated? The answer to this question will differ with the nature of the neoplastic disease under consideration and the probability of obtaining a beneficial response with the drugs available. The information contained in Tabs. 1 through 4 will be helpful in making judgments of this kind. Obviously, chemotherapists are more inclined to favor early drug therapy when a "new" drug or an improved regimen for an "old" drug is known to be less productive of undesirable toxicity, more frequently effective and more likely to prolong survival. As an example of this possibility for improved results due to early therapy with an "old" drug, the experiences of Dr. Wayne Rundles of Duke University should be quoted (Pers. Commun.). Dr. Rundles has demonstrated that if chlorambucil treatment is initiated immediately after the diagnosis of chronic lymphocytic leukemia has been established, approximately 80% of patients with this disease are alive 5 years later. Of those chronic lymphocytic leukemia patients whose treatment with chlorambucil was delayed until the classical indications of accelerated disease appeared, Dr. Rundles found that only about 20% survived 5 years after diagnosis. This impressive improvement in survival with early oncolytic drug therapy should inspire early use of oncolytic drugs for the treatment of other malignant diseases, particularly those which are classically left untreated until deterioration occurs.

A twelve weeks' trial of therapy is often necessary to determine whether or not a carcinoma is going to respond to an oncolytic drug. However, with the leukemias and the lymphomas, the outcome of drug treatment is usually apparent after 6 weeks' trial. Most chemotherapists now agree that, after a beneficial response has been obtained, oncolytic drug therapy should be continued for so long as a beneficial response can be maintained.

Tab. 5 illustrates the need for modifying the dosage regimen of an oncolytic drug both according to the nature of the disease being treated and according to the duration of the drug therapy. Thus, for acute childhood leukemia, large weekly doses of vincristine sulfate (in combination with large daily doses of steroids) are given for a short time until remission has been induced. Thereafter, the use of both vincristine sulfate and steroids is discontinued and other drugs (methotrexate, 6 mercaptopurine or

Tab. 5. Vincristine sulfate (Oncovin) dosages

1. *Acute Childhood Leukemia*

   A. For remission *induction* (in combination with Prednisone)
   0.05 — 0.15 Mg/Kg/Week I. V.
   (2 Mg/M²/Week I. V.)

   B. Not recommended for remission *maintenance*

2. *Other Malignancies (Children and Adults)*

   A. 0.025 Mg/Kg/Week I. V. initially until benefit obtained, then:

   B. 0.005 — 0.010 Mg/Kg/Week I. V. (as tolerated) for maintenance

cyclophosphamide) are employed for the maintenance of the remission. After each relapse, the combination of vincristine sulfate and steroids may again be used temporarily to induce another remission (Selwary *et al.*, 1965). Much smaller weekly doses of vincristine sulfate than are necessary for remission-induction in childhood leukemia may be employed for the treatment of lymphomas and carcinomas (Tab. 5). For the latter types of tumor, vincristine sulfate is given weekly in relatively small and non-toxic doses for so long as benefit can be maintained (Finkel and Yount, 1966).

Tab. 6 summarizes the better results which can be obtained in the maintenance of remission from childhood leukemia when methotrexate is given intramuscularly in doses of 30 mg/m² twice weekly as compared with the results obtained in this disease when conventional doses of 3 mg/m² by mouth daily are employed (Selwary *et al.*, 1965). Both of these dosage regimens produce comparable "maximum permissible" toxicity. However, it has been postulated that the twice weekly regimen is more ef-

Tab. 6. Methotrexate in acute childhood leukemia

Conventional Method:
3 Mg/M²/Day P.O.
Gives 3.3 months median duration of remission

Experimental Method*:
30 Mg/M²/2 times per week I. M.
Gives 17.0 months median duration of remission

* Acute Leukemia Group B. *J.A.M.A.*, **194:** 187-193, 1965

fective than the daily regimen because it permits the body's "immune defense mechanisms" to recover between doses.

In contrast to the above experiences with methotrexate, J. F. Holland *et al.*, have found cyclophosphamide to be more effective in prolonging remissions from childhood leukemia when it is given in smaller and less toxic doses than are considered conventional. Thus, weekly intravenous doses of 600 mg/m² have been found more effective in this regard than have doses of 1000 mg/m².

Modification of cyclophosphamide dosage may also be advantageous in the treatment of lymphomas and carcinomas. Foley and Kennedy (1964) have recently demonstrated that doses of 15 mg/kg (approximately 600 mg/m²) once weekly are at least as effective for such malignancies as are conventional doses, i.e.: 5 mg/kg/day by mouth or intravenously (Tab. 7).

Conventionally, 5 fluorouracil has been given in repeated courses of daily 15 mg/kg intravenous injections once every 4 to 6 weeks, each course being carried to toxicity. At present, some chemotherapists in the U.S.A. (Louis, Pers. Commun.) are investigating the use of 5 fluorouracil in less toxic dosage. After an initial 5-days' course of 12 mg/kg/day I. V., these investigators are thereafter injecting only one dose of 6-12 mg/kg (depending on tolerance) once every 7 days on a maintenance basis

Tab. 7. Cyclophosphamide in treatment of lymphomas and carcinomas

Conventional Dosage:
5 Mg/Kg/Day P. O. or I. V.

Experimental Dosage*:
15 Mg/Kg Once Every Week I. V.
or
7.5 Mg/Kg Once Every Week I. V.
(If Leukocyte Count Below 5000/Cu. Mm.
Or Thrombocyte Count Below 150000/Cu. Mm.

* J. F. Foley and B. J. Kennedy, *Cancer Chemotherapy Reports*, **34:** 55-58, 1964.

(Tab. 8). This new regimen appears to be considerably less toxic and possibly no less effective than the conventional regimen. However, more data than is at present available will have to be obtained before a firm comparison of the effectiveness of these two regimens can be made.

Chemotherapy may also have a place in preparing cancer patients for surgery. In this context, D. H. James and others (1964) have described the use of vincristine sulfate in rendering inoperable tumors operable.

One must bear in mind the possibility that the use of oncolytic drugs in the maximum permissible dosage may not necessarily be more effective than the use of smaller doses. Obviously, excessive doses are undesirable but when the effects of two dosage magnitudes are compared, neither being productive of toxicity, the lesser

Tab. 8. 5 Fluorouracil in the treatment of carcinomas

Conventional Dosage:
Courses of 15 Mg/Kg daily I. V. for 5 days
Then 7.5 Mg/Kg every 2nd day to toxicity
Repeat courses every 4-6 weeks as permitted by recovery from toxicity
Experimental Dosage:
" Loading " course of 12 Mg/Kg I. V. for 5 days
Then 0.5 — 1.0 Gm/week (total dose) as permitted by blood counts

dosage, in the case of some drugs, may prove to be more effective in prolonging remission than the larger dosage (e. g., cyclophosphamide in acute childhood leukemia).

Dr. Denis Burkitt in Uganda has recently demonstrated that several of his African lymphoma patients have been " cured " following only one or two small doses of cyclophosphamide, whereas, usually, only temporary remissions followed the use of conventional " heavier " courses of cyclophosphamide therapy in which larger doses were applied for a longer time.

The philosophy that small doses of oncolytic drugs may be more effective in treating malignant diseases than are larger doses is obviously at variance with the school of thought which suggests the need for a " total kill " of malignant cells with a combination of several oncolytic drugs, each given in maximum possible dosage. Such combination chemotherapy has undoubtedly produced better rates and durations of remission in acute childhood leukemia than has sequential therapy with the same drugs. However, it has not produced " cures " of leukemia and the toxicity encountered has been formidable. In this context, it is interesting to note that some investigators now believe that the better results which have been obtained in treating acute leukemia with combination chemotherapy may be related to the combination of drugs *per se* rather than to specific dose levels and schedules or to the induction of a high degree of toxicity (Thompson *et al.*, 1965).

Conclusions

Cancer in children has a better chance of being " cured " with oncolytic drugs than does cancer in adults. For this reason in cases of malignant disease in childhood, there is need for a sequential trial of therapy with, if necessary, every appropriate oncolytic drug available. Combinations of these drugs given simultaneously have been advantageous in some cases.

For some types of disseminated malignant disease, oncolytic drug therapy has, traditionally, been delayed until the patient's malignancy has become very advanced and causing gross symptoms. In such cases a drug has little chance of prolonging survival and usually does not achieve more than temporary palliation for some of the cases. Severity of side-effects and relative ineffectiveness have been given as the reason for such delayed therapy, it being said that drug treatment can be more troublesome to the patient than his disease in its earlier stages. The administration of smaller and nontoxic doses of these drugs at weekly intervals is under investigation. Should such new regimens prove to be not less effective than the traditional, larger and toxicity-producing courses of daily doses, earlier treatment would then be justifiable. Theoretically, earlier treatment might be expected to maintain a patient in good condition for a longer time and, possibly, might also be more frequently effective.

The use of small, nontoxic and more widely spaced doses might also be expected to be less damaging to a patient's immune defense mechanisms. Possibly such defense mechanisms may also help the patient not only to combat infection but also to control the advance of his malignant disease.

Although better therapeutic results and less toxicity have been obtained in some malignancies when an oncolytic drug has been administered in less than " conventional " dosage, it is not the author's intention to recommend that all oncolytic drugs be administered in this manner for all types of cancer. It is recognized that there is a need to vary the dosage magnitude and frequency of some drugs depending on the type of malignancy being treated.

There are two schools of thought concerning the drug treatment of acute childhood leukemia. One school postulates the need for using the maximum possible dosage of all effective drugs in combination in an attempt to achieve a " total kill " of the malignant cells in the body. The other school believes that such massive therapy is too injurious to the host and that it would not necessarily eradicate the cause of the malignancy. This latter school postulates that combination chemotherapy may have some advantage over sequential therapy but that this advantage may well be due to the combination of drugs *per se* rather than to specific dose levels and schedules which produce a high degree of toxicity.

Many unresolved problems continue to beset the cancer chemotherapist and, with few exceptions, oncolytic drug therapy is usually not curative for adult cancer patients. It, therefore, behooves us to search constantly for improved methods of administering the currently available oncolytic drugs and to avoid the assumption that traditional methods are necessarily the best.

Summary

1. Lists have been made of the more frequently occurring malignant diseases and of those commonly available oncolytic drugs which, in the author's opinion, are most appropriate for their treatment.

2. Those tumors which do not usually respond to oncolytic drugs have also been listed.

3. For several malignant diseases it has been found that small doses of oncolytic drugs have proved just as effective for inducing remission and even more effective in prolonging remission than have larger doses of these drugs. The explanation for this may be that smaller doses do less harm to the body's immune defense mechanism than do larger doses.

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RIASSUNTO

1. Vengono passate in rassegna le malattie tumorali più frequenti ed i medicamenti oncolitici normalmente disponibili, considerati come i più appropriati nel loro trattamento.

2. Sono stati anche indicati quei tumori che generalmente non reagiscono ai medicamenti oncolitici.

3. Per molte malattie tumorali è stato trovato che piccole dosi di medicamenti oncolitici sono risultate altrettanto efficaci nell'indurre la remissione, ed ancor più efficaci nel prolungarla, che non dosi maggiori. Ciò può essere interpretato in termini di un minor danno ai meccanismi immunitari di difesa dell'organismo.

RÉSUMÉ

1. Les maladies tumorales les plus fréquentes ainsi que les médicaments oncolytiques normalement disponibles considérés appropriés dans leur traitement sont passés en revue.

2. Les tumeurs qui généralement ne répondent pas aux médicaments oncolytiques ont aussi été indiquées.

3. Pour bien des maladies tumorales il a été trouvé que de petites doses de médicaments oncolytiques peuvent résulter autant efficaces dans l'induction de la rémission, et même plus efficaces dans son prolonguement, vis-à-vis de doses plus élevées. Ceci peut être expliqué par le fait que les doses moins élevées sont moins nuisibles pour les méchanismes immunitaires de défense de l'organisme.

ZUSAMMENFASSUNG

1. Übersicht über die häufigsten malignen Erkrankungen und die normalerweise verfügbaren onkolytischen Medikamente, unter Berücksichtigung ihrer jeweiligen Indikation.

2. Angabe der Tumoren, die allgemein nicht auf die onkolytischen Medikamente ansprechen.

3. Bei vielen malignen Erkrankungen wurde festgestellt, dass geringe Dosen onkolytischer Medikamente ebenso wirksam sind, um eine Besserung zu erreichen, und sogar noch wirksamer, um diese zu verlängern, als höhere Dosen. Das scheint dafür zu sprechen, dass die immunitären Abwehrmechanismen im Organismus durch geringere Dosen weniger geschädigt werden.

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