1966

Review of the program for the investigation of cancer chemotherapeutic agents at the University of Nebraska, College of Medicine

Charles William Newman
University of Nebraska Medical Center

REVIEW OF THE PROGRAM FOR THE INVESTIGATION OF CANCER CHEMOTHERAPEUTIC AGENTS AT THE UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE

Charles William Newman

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

January 8, 1966

Omaha, Nebraska

TABLE OF CONTENTS

Page

I. Introduction 1

II. History of the Clinical Drug i:raluation Program 2

A. National organizatibn

B. The program at University Hospital

III. Drugs used in the program 8

A. Methotre-xate

B. Alanine Mustard

C. NSC-1026

p. Oxylone

E. Hexamethylmelamine

F. Hexestrol

G. NSC-172.56 E

H. Actincmycin D

IV. Review of patients treated at University Eospital 14

A. Patients treated with Alanine Mustard

B. Patients treated with Methotrexate

C. Patients treated with Hexamethylmelamine

D. Patients treated with NSC-1026

E. Patients treated with Oxylone

F. Patient treated with Hexestrol

V. Summary 35

Acknowledgements 37

INTRODUCTION

In selecting a topic for a paper such as the senior thesis, it is desirable to pick one which will be informative and of interest to the writer and to members of the faculty who donate their time to assist with these projects. If this is kept in mind I believe that the time spent on such an effort is certainly much better utilized.

In deciding on a topic, it seemed to make more sense to review some aspect of medicine which is near at hand as opposed to reviewing literature produced in some distant place. With these things in mind I decided to review, from its inception to the present time, the Clinical Drug Evaluation Program which has been in operation at the University of Nebraska Hospital for several years. In reviewing a program such as this it can not be expected that concrete conclusions can be drawn on such matters as increase in survival time of a person with a certain tumor who is treated with a certain drug, but it is certainly possible to give an over-all view of the general effects of these drugs. It is also possible to relay the clinical impressions as to whether

these persons were made more comfortable during their remaining months and, if so, to speculate on the value of the treatment. Attempts to cope with the ravages of cancer are often times desperate, and this is certainly understandable when dealing with a disease which has been as refractory to medical advance as has mitotic disease.

In this review, it is of interest to relate briefly the history of the program with special emphasis on the aspects of it at this institution. It is also necessary to go into a few of the details regarding the drugs used in the program with a small part given to history of each drug and the remainder given to chemical properties, toxicity etc. The rest of the paper will deal with the patients, case by case, with an attempt being made to group them as to the type of drug used.

HISTORY

The Clinical Drug Evaluation Program was designed for the investigation of chemotherapeutic agents as they are used in treating the so-called solid tumors. The program on a national basis is of two phases. Phase one of the study is to attempt to arrive at a

dosage schedule and to try to determine the side effects. The dosage schedule is to be such that the patients will be brought to maximum tolerated but still reversible toxicity over a period of six to eight weeks. In the initial exploration of dosage, the starting dose can be 1/100 to 1/50 of the LD_{50} in the dog or monkey. This dose can be doubled at two-week intervals until the first sign of toxicity appears. While exploring these dosage requirements, various routes and rates of administration can also be investigated.

In the phase two studies, evidence of antitumor activity is sought in a wide variety of tumor types with the criteria for evaluation of response to be explained in more detail later. It is of note that in this phase of the study the sample size is to depend upon the degree of antitumor activity being sought. For example, if a 20% response rate is sought with a 5% acceptance error, then the drug can be rejected if there are 18 nonresponders. Phase two is set up with various stipulations as to selection of patients, evaluation of results etc. All investigators have to agree to follow the rigid protocol as set up by the central committee. A summary of this protocol is

presented on the following pages.

1. There has to be histologic proof of incurable cancer with slides available for reference.
2. One or more of the following means for measuring tumor mass has to be present.
   a. There has to be a palpable tumor mass with well defined margins allowing direct measurement.
   b. The tumor margins outlined by X-ray must be such that they can be easily measured.
   c. The tumor may have a specific biochemical abnormality which can be accurately measured quantitatively.
3. The patient must be at least fifteen years old.
4. There may have been no therapy with similar agents.
5. No patient can be entered into the program until four weeks after discontinuance of previous cancer chemotheraphy and then only if there is no evidence of continuing toxicity from previous treatment.
6. Patients who have failed to respond to pre-

vious therapy may be entered when they have developed new metastases or when lesions present have increased in size by 25%.

7. Patients who have had a response to previous therapy must have objective evidence of a relapse. For instance, there may be a 25% or more increase in the size of the lesion present.
8. Patients on steroids for treatment of other conditions may be entered on the study provided major dosage changes are not made.
9. Patients who have had adrenalectomies or hypophysectomies are not acceptable to the program.
10. Patients who have had radiotherapy may not be placed on the program until four weeks after therapy has been completed. In addition, patients who have had radiotherapy must show progression of disease before they can be placed on the program.
11. A patient who has a serious infection, is actively bleeding, or has an associated severe systemic disease should not be entered on the program.

12. The patient should have an estimated life expectancy of at least three months.

13. The white blood count must be greater than 4,500, platelets must be above 150,000 and B.U.N. must be below 25 mg%.

14. The patient is to be on no concomitant drug therapy which may have an effect on the tumor.

15. There should be no planned palliative procedures within the next three months.

There are also criteria present for adjudication of adequacy of treatment and are as follow: Duration of therapy must be adequate, and it is further stipulated that unequivocal toxicity must be produced to prove that dosage has been adequate. The period from the start of therapy through the period of toxicity must be at least six weeks with an additional two weeks for observation.

It is readily seen that the above stipulations are essential if a study of this type is to achieve any degree of objectivity. It is to be noted that patients who do not meet the above requirements are not denied the possible benefits of chemotherapy but are simply not placed in the study group. It can also be seen that in order to comply with this selectivity,

many more patients are needed and, here again, problems are encountered as each hospital participating in the study is expected to bring a certain minimum number of patients into the study each year.

As noted above, the program was divided into two phases. Phase one was developed with a minimal number of patient trials and was designed to establish dosages and investigate toxicity. It was very necessary to know something of the toxic reactions which might occur so that they could be watched for and coped with when the drugs were used on large numbers of cancer victims.

The University of Nebraska College of Medicine was not connected with phase one of the project since it was a limited type study and had been in progress for some time before this institution became involved. First, communication concerning phase two was received in April of 1961, and was in the form of a letter from Dr. Curreri who is chairman of the Central Region of the Chemotherapy Cooperative Group. Due to a lack of funds in the program at that time, active participation at the College of Medicine did not get under way until late in 1961. Dr. Musselman was the

first named investigator at Nebraska and a short time later Dr. Daniel Miller was also designated an investigator in the program. Several years later, upon finishing his surgery residency at University Hospital, Dr. Robert Westfall became involved in the program and is now taking a very active part.

As with any other complex investigative program, the Clinical Drug Evaluation Program has had its growing pains, both here and in the other areas. The necessity for the multitude of clinical evaluations to be categorized so that they can be assimilated by computers poses quite a problem.

DRUGS

It is of interest to offer a brief discussion of the drugs used in the program. I believe a detailed discussion is a bit frilly since many of the experimental drugs lose favor with about the rapidity as do women's hats. It is necessary, however, to give a little history where possible, the probable mechanism of action, a few of the properties and the manifestations of toxicity thus far encountered. The drugs will be discussed in no particular order. The dosages and dosage schedules will be given first in the interest of

accessibility for reference, and will be followed by more discussion of each drug.

Methotrexate: This drug is given via the I.V. route and is begun with a primary dose of .2 mg./kg. per day for four days. Regardless of weight, the dose is not to exceed 15 mg. per day. A continuation dose of .1 mg./kg. per day is given for eight days. This is not to exceed 7.5 mg. per day regardless of weight. A second course may be begun on day 42.

Alanine Mustard: The route of administration is by I.V. using 5% dextrose and water as a vehicle. A dose of 1.6 mg./kg. is given once weekly for six weeks. Two six-week courses may be given.

NSC-1026: This drug is given I.V. over a one-hour period at a dosage of 300 mg./kg. per day. The first course consists of daily administration for eight days. This course is followed by a 28 day observation period after which the same dosage is given for seven consecutive days.

Oxylone: This drug is given orally at a dosage of 25 mg. B.I.D. for eight weeks.

Hexamethylmelamine: The oral route is used for

this drug, about 15 mg./kg. per day is given in four equal doses.

Hexestrol: This drug is given orally after breakfast and at bedtime at a dosage of one gram on each occasion, and is given for eight successive weeks.

NSC-17256: This drug is given 100 mg. B.I.D. orally for eight weeks.

Actinomycin D: The drug is given I.V. either daily or every two days at a dosage of 12 mcg./kg. per day for five consecutive days. One day is then skipped and on the next day a dosage of 8 mcg./kg. per day every other day is given until toxicity is reached. No more than four of these dosages are given.

With some of the above drugs the duration of therapy is not given as this may be adjusted to the situation.

Methotrexate: (MTX, A-Methopterin) This drug has been used with limited success in the treatment of certain solid tumors and with good results in the treatment of chorio-carcinoma. With these plus factors in mind it was decided to give the drug a more extensive clinical trial. The basic mechanism of

action of this drug is the inhibition of nucleotide synthesis through the antagonism of folic acid. It is of note that folic acid is converted to citrovorum factor which is associated with essential enzymatic activity. Using this rationale, citrovorum factor can be used as an "antidote" for methotrexate. The compound is soluble in alkali and acid but insoluble in water and organic solvents. The drug is rapidly absorbed from the G.I. tract and is excreted unchanged. Toxic manifestations are: nausea, vomiting, abdominal pain, buccal and pharyngeal ulceration, diarrhea, leukopenia, thrombocytopenia, macrocytosis, anemia, rash, and alopecia. There must be adequate fluid intake if the drug is to be used.

Alanine Mustard: This drug is, of course, in the nitrogen mustard group of alkylating agents and first experiments as to its effects on tumors were conducted in 1942-1943. The nitrogen mustards were first used as war gases and were noted for their extreme toxicity. It was discovered that alanine mustard had a selective action against tumor cells but was about 18 times less toxic than nitrogen mustard. It was also discovered that alanine mustard had very little cutaneous vesicant action. Variations of the

drug have been: TEPA, TEM, TSPA, Myleran, Chlorambucil, and Nitram.

The drug achieves its action through the introduction of alkyl radicals into various biologic materials by the ethylene immonium cation. The drug does not interfere with the biosynthesis of nucleic acids but reacts directly with formed nucleic acids. Phlebitis is the main problem in administration of the drug. Toxic manifestations are: Nausea, vomiting, leukopenia, and anemia.

NSC-1026: This drug is a simple five membered carbon ring with NH_2 and COOH at one of the carbons. The remainder of the valencies are occupied by hydrogen ions. The compound is soluble in water to the extent of about five grams to one hundred grams of water. It is soluble in diluted acid and alkali. The proposed mechanism of action is possibly through the antagonistic action to valine but this is not established with certainty. The main toxic manifestation is neurologic degeneration whereby acute and permanent degeneration of the spinal cord and peripheral nerves may occur.

Oxylone: (NSC-33001) Oxylone is a synthetic steroid

with corticoid and progestational activity. As with all steroids the basic mechanism of action is unknown. The drug is readily absorbed following oral administration and it or its metabolites are rapidly excreted. The drug has thus far shown effectiveness against metastatic breast cancer and osseous metastases. Toxic manifestations have primarily been cushinoid swelling of the facies. There has also been some incidence of peptic ulceration and aggravation of hypertensive states.

Hexamethylmelamine: (NSC-13875) This drug is quite similar to triethylenemalamine structurally but the mechanism of action is possibly through the dehydrogenation of the methylolamino or oxidation of the methylmethylolamino side chains. The second is the more probable. The toxic reactions are the same as those of other alkylating agents with the reticulocytopenia being most prominent. In autopsies, pulmonary edema and hemorrhagic pulmonary lesions have been noted.

Hexestrol: This drug is a synthetic steroid with very potent estrogenic activity. Again the mechanism of action is a mystery. Weight loss has been noted with

intensive use of the drug and other side effects have been dermatitis, gingivitis and ocular hemorrhages.

NSC 17256 E: This is another synthetic steroid and has had limited usage in the treatment of breast cancer. Toxic manifestations are much the same as those of Hexestrol.

Actinomycin D: This is one of a number of antibiotics produced by the Streptomyces group of organisms. The rationale for the mechanism of action is that this compound forms tight reversible complexes with DNA. It is of note that guanine must be present in a DNA preparation in order for this complex formation to take place. Toxic manifestations are nausea, vomiting, diarrhea, anorrexia, oral ulceration, skin pigmentation, leukopenia, thrombocytopenia and occasional alopecia. There is also local necrosis if the drug is given subcutaneously or intramuscularly.

CASE REVIEWS

In the following pages it will be attempted to summarize the case histories of patients who have been treated with anticancer drugs at the University of Nebraska Hospital. The mechanics of this undertaking

are a problem in that one must do justice to reviewing each case in the shortest space. I believe a short paragraph giving the pertinent details of each case will suffice as opposed to placing them in tabular form. The patients will be referred to by initials only.

The following patients were all treated with Alanine Mustard:

C.B.: The primary tumor in this case was a squamous cell carcinoma of the left hypopharynx which was discovered after enlarged cervical nodes were noted. This patient was originally treated by left radical neck dissection followed by irradiation. There was subsequent recurrence of disease and a node in the area was used in judging efficacy of treatment. This man had severe nausea and vomiting when given the drug and the dose had to be reduced. The node increased in size by about one inch during the course of therapy and became ulcerated. The patient's course was steadily downhill and as noted there was no response by the tumor.

E.K.: The primary tumor here was a squamous cell carcinoma of the left bronchus which was biopsied

through a bronchoscope. A full course of drug therapy was given without complications. Two areas were followed by X-ray and both decreased in size by about one half inch during the course of therapy.

R.W.: This man had a clear cell carcinoma of the kidney which was at first attacked surgically with rather wide removal of disease. Within four months pulmonary metastases were noted and tumor mass was palpated elsewhere in the body. A full drug course was given with the patient experiencing rather severe nausea and flatulence during much of the course. There was no decrease in lesion size during therapy and the patient expired about one year after the tumor was discovered.

G.S.: This man had carcinoma of the stomach and esophagus and was given a full course of drug therapy. Various nodes were measured during therapy and all steadily increased in size. The course of the disease was progressive and the patient died five months after the tumor was discovered.

J.K.: In this case, a transitional cell carcinoma of the urinary bladder was the original tumor. Drug therapy was started and very soon the patient became

so weak that he could not stand. It was supposed that this was due to the drug and a full course was not completed. Mental confusion developed and cerebral metastases were suspected. The patient died of bronchopneumonia four months after diagnosis was made.

C.R.: This man had a squamous cell carcinoma of the mouth and alanine mustard was given although no fair trial was obtained as the patient died of a massive pulmonary embolism just seven days after the drug was started.

R.S.: This was a case of widely disseminated lymphosarcoma. The drug was begun and due to a lack of suitable veins one or two intraarterial injections were given, with the latter resulting in the artery's becoming sclerosed. There was no change in the size of the tumor areas being measured and this man was dead within two months after the disease was diagnosed.

L.N.: This woman had squamous cell carcinoma of the cervix with metastases to the lungs. During the course of therapy some nausea and vomiting were encountered, although not severe. Here again, the measured lesions steadily increased in size and the

course was rapidly downhill.

Summary: This is admittedly a very scant number of patients treated with this drug and obviously it would be foolish to try to draw any conclusions. There were several instances of rather severe reaction to the drug. The main complaint was nausea and vomiting. In all but one case there was a measureable decrease in the size of lesions. This was in the case of a primary squamous cell carcinoma of the lung.

The following patients were treated with Methotrexate:

F.H.: This 53-year old man had a bronchogenic carcinoma which was histologically diagnosed at the time of his thoracotomy. As first treatment he was given irradiation to the extent of 4,236 r to the area. This was followed by a course of therapy with an anti-metabolite. The above therapy provided very little in the way of benefit and methotrexate was begun; again, little response was noted although the man had no ill effects from the drug. Death occurred about 6½ months after the diagnosis was made.

J.K.: This man had a poorly differentiated squamous cell carcinoma of the left upper lobe with extension to the chest wall. During the course of therapy the white blood cells dropped to 2,400 per cubic millimeter and the platelets dropped to 25,000 per cubic millimeter. Severe G.I. bleeding occurred and ten units of blood were required; this was to no avail and the patient expired. During therapy there was no decrease in tumor size and the therapy was adjudged as being ineffective.

N.W.: This 62-year old woman had a poorly differentiated sarcoma of unknown primary location. When diagnosed, she had subcutaneous nodules, pulmonary metastases and a retroperitoneal mass. The patient had had a previous adenocarcinoma of the endometrium which was treated by radical surgery. One course of therapy was given and the readily measurable nodules continued a steady increase in size. No toxicity was manifested.

A.V.: This man had a poorly differentiated reticulum cell sarcoma of the right thigh which was incompletely excised by his local physician. Following this, he had irradiation to the area to the

extent of 6,000 r with no regression of tumor. Chemotherapy was begun but on the fourth day the patient developed severe stomatitis and the next three doses had to be given over a prolonged period. The mouth and throat lesions healed following therapy. A lesion in the axilla was noted to increase in size by about 3/4 inches and response was adjudged as negligible.

H.S.: This 70-year old man had a sarcoma, which was probably an angiosarcoma, located in both lungs. There were no complications to the drug, but response was again negligible and the patient died about two months after the diagnosis was made.

G.B.: This 58-year old woman had a leiomyosarcoma of the uterus which was of considerable size before help was sought. After three doses of the drug she developed severe stomatitis and the drug had to be discontinued. The tumor was increasing rapidly in size and many pressure problems were soon to develop.

E.F.: This 76-year old man had an adenocarcinoma of the stomach diagnosed at the time of celiotomy. During the course of therapy, there was clinical improvement but the measured mass continued to increase

in size. The last day of therapy the patient became very weak and died two days later.

D.H.: This 50-year old man had a squamous cell carcinoma of the larynx for which a total laryngectomy with a radical neck dissection was performed. About nine months after this, nodes were discovered in the neck and were shown to be metastatic carcinoma. At about this time neurological and behavioral changes were noted and brain metastases were suspected, although never proved. The drug was well tolerated and the mental status improved although the nodes continued to grow. Death occurred in about one month.

A.L.: This 60-year old man had a primary adenocarcinoma of the small bowel with massive liver metastases proven at time of the celiotomy. A full course of drug therapy was given without complications. The course was rapidly downhill and the patient was dead within one month.

N.H.: This 23-year old woman had an osteogenic sarcoma of the jaw with metastases to both lungs from which considerable chest pain resulted. During the therapy the pain was reduced but the lesions stayed the same. At the end of therapy the patient was doing

well although the prognosis was, of course, very guarded.

I.C.: This 56-year old man had his left eye enucleated in 1944 for what was diagnosed as a malignant melanoma. During the present hospitalization, an abdominal mass was discovered and a subsequent celiotomy showed melanoma metastatic to the liver and mesenteric lymph nodes. Two courses of methotrexate were given with no ill effects. In the three months following the chemotherapy the abdominal mass, which was serving as the guide as to efficacy of therapy, enlarged an estimated eight centimeters. It was the observers' opinion that neither subjective nor objective benefit was in evidence.

R.S.: This 62-year old man had a poorly differentiated adenocarcinoma of the lung with extension to the cervical tissues. At the time chemotherapy was begun, the patient was experiencing considerable pain from his disease. Within five days after therapy was begun the patient was subjectively much improved, although there was no decrease in the size of the measured lesions. After the first course of therapy the pain resumed but was benefited by the

second course of therapy. The lesions continued to increase in size and numerous osseous metastases developed so that the patient's condition was rapidly deteriorating by the end of the second course of therapy.

T.R.: This 57-year old man had an epidermoid carcinoma the primary site of which was not discerned. It was noted that three years previously he had surgical treatment for a transitional cell carcinoma of the urinary bladder. The epidermoid presented as a mass in the right neck with hoarseness which had been present for about a month. A full course of therapy was given without complications. About 1½ months after the diagnosis was made, the lesion had become large and fungating and the brachial plexus was involved by tumor. No response was obtained.

G.S.: This man presented with a rapidly growing mass on his tongue which he had first noted six weeks before entering the hospital. The lesion was diagnosed as being a rhabdomyosarcoma and a partial glossectomy was performed. Two weeks later, chemotherapy was begun and at this time a lesion was noted in the left upper lobe and there was a mass, which

was subsequently demonstrated as being metastatic tumor, in the left deltoid area. No problems were encountered during therapy but one day after its completion the patient developed a severe stomatitis and a toxic cutaneous rash which subsequently became an exfoliative dermatitis. During therapy there was a slight decrease in the size of the deltoid mass but soon after therapy was completed all lesions were noted to be rapidly enlarging.

C.J.: This 74-year old man had a mixed mesodermal sarcoma which was of unknown primary origin but presented as a large mediastinal mass. Tumor mass was also soon to develop in the neck. Toward the end of the first course of therapy, the patient developed a mucositis of the upper G.I. tract and numerous furuncles developed on the face. During the first course there was subjective improvement and since the mucositis and furuncles responded to conservative treatment it was decided to give a second course of the drug. After only three doses of the drug the patient developed a large mouth ulcer and the drug was discontinued. Soon after this, the patient showed much improvement and the neck mass completely disappeared, although the size of the

mediastinal mass remained unchanged.

K.C.: This 54-year old woman developed a transitional cell carcinoma of the left renal pelvis for which a nephrectomy was performed 2½ years before being seen at University of Nebraska Hospital. At the time of her appearance here, she had a mass in the left flank which was histologically consistent with a diagnosis of metastases from the renal carcinoma. Chemotherapy was begun but the patient died of a massive myocardial infarction after receiving only two doses of the drug.

Summary: As observed on the preceding pages, sixteen patients with about fourteen tumor types were treated with methotrexate at University Hospital. It can not be overly emphasized that all the patients treated in this program had far advanced disease and all other forms of therapy had proved ineffective. There was somewhat of a range in toxic manifestations observed including stomatitis, leukocytopenia, and thrombocytopenia, and, as a result, bleeding episodes and infection were encountered. There was also one case of a toxic dermatitis which subsequently became an exfoliative type of dermatitis.

Again this is a very limited number of trials to try to draw any conclusions from but some indication as to beneficial results can be summarized as follows:

In one case the patient had an adenocarcinoma of the stomach with a large tumor mass and considerable symptoms. During therapy there was relief of symptoms for a time, although there was no change in the size of the tumor mass. Another man had a carcinoma of the larynx for which radical surgery was performed but who developed local metastases and suspected brain metastases with behavioral and neurologic abnormalities. During the course of drug therapy the mental status improved, although the improvement was brief and the disease ran its course. A young woman with an osteogenic sarcoma of the jaw with metastases in both lungs and considerable pain from these lesions was given a full course of methotrexate. During therapy the pain was much reduced but the lesions did not change in size. The patient was doing quite well at the end of the study period but the prognosis was very guarded. Also to benefit from drug therapy was a 62-year old man who had a poorly differentiated adenocarcinoma of the lung and who was having considerable pain from his disease. Within five days after therapy was

begun the pain was much diminished but the lesions remained unchanged. After the first course the pain again became severe but was again diminished by the second course of the drug. During the second course bone metastases were noted and the patient's condition was rapidly deteriorating. The last patient of this series to benefit from treatment had a mixed mesodermal sarcoma, the primary site of which was unknown. When first seen he had a large mediastinal mass and a mass soon developed in the neck. During the first course of therapy he developed a mucositis and furuncles on his face. These healed and a second course was started only to have the patient develop a large stomal ulcer. The drug was discontinued but at this time it was noted that the neck mass had completely disappeared, although the mediastinal mass remained unchanged. In this case the results were somewhat equivocal but it was assumed that the resolution of tumor mass was due to the drug.

The response to methotrexate as noted above was a random thing but in certain cases was certainly worthwhile as the cancer victim was made more comfortable, at least for a time. There were certain bad side effects and, on the other hand, this tends

to speak against the drug therapy.

The following patients were treated with Hexamethylmelamine:

D.J.: This 38-year old man had a teratocarcinoma of the right testis with metastases to the inguinal lymph nodes. An orchiectomy with node dissection was done but soon metastases were again noted in the area. During the course of therapy the patient had moderate nausea. The pain from the neoplasm remained unchanged. No benefit was derived and the course was rapidly fatal.

C.J.: This 75-year old man had a mesodermal sarcoma of unknown primary origin. He had been treated with methotrexate ten months earlier with some response. At the time he was treated with hexamethylmelamine he had a large mediastinal mass and pre and subauricular masses. During therapy he had moderate to severe vomiting and, in brief, all results from the drug were negative as the neoplastic process proceeded unchecked.

G.D.: This patient had an adenocarcinoma of the right kidney metastatic to the lungs. The

patient had noted symptoms about one and one half months before seeking help and this amounted to two and one half months before drug therapy was instituted. The patient tolerated the drug very well but the lung lesions continued to grow and so far as could be discerned the treatment was a failure.

I.C.: This 56-year old man had a malignant melanoma of the left eye for which that eye was removed in 1944. He presented at this hospital with a large abdominal mass and metastatic nodules in the liver as proven at the time of his celiotomy. He was given full courses of methotrexate and 6-MP without result. Hexamethylmelamine was begun but the patient died 18 days later and the effort was, of course, classified as futile.

M.S.: This 67-year old woman had an adenocarcinoma of the left lung. During the course of therapy the patient had mild anorexia but not to the extent that the drug had to be discontinued. There was a steady increase in the size of the lesion and the course was progressively downhill.

R.S.: This 64-year old woman had an anaplastic carcinoma of the lung. During therapy moderate

anorexia and severe vomiting were encountered and the drug had to be discontinued after thirteen days but, during this period, a new lesion was encountered in the lung.

T.M.: This 68-year old man had an anaplastic carcinoma of the right lung. The drug was given but severe anorexia and vomiting developed and it had to be discontinued after only seven days.

H.B.: This 70-year old man had a squamous cell carcinoma of the left tonsil with cervical metastases. During therapy moderate anorexia and vomiting occurred but the drug was continued. During this time the size of the cervical mass increased by about one centimeter but in the following month the mass decreased in size by about two centimeters in all dimensions. This was the situation present at the end of the study period and it was felt that a response had been obtained.

V.M.: This 57-year old woman had an adenocarcinoma of the gallbladder diagnosed in May of 1963 at which time a cholecystectomy was performed. Obstruction occurred and a gastrojejunostomy was performed in January of 1965. A sub-hepatic mass was followed as a guide to drug efficacy. The drug was

taken without difficulty and the mass decreased in size by three centimeters in one dimension and four centimeters in the other. After the drug was withdrawn, the mass resumed its growth and since that time other procedures have been done to relieve the ensuing obstruction.

Summary: In all, nine patients were treated with this drug and it is evident that nausea, vomiting and anorexia were the major side effects as one, two or all of these were seen in varying degrees of severity in six of the patients. In two of the patients, the reactions were severe enough to necessitate withdrawal of the drug. A response was obtained in two of the cases. The first was in a man with an anaplastic carcinoma of the lung with cervical metastases. The second was in the case of a woman with adenocarcinoma of the gallbladder where a considerable decrease in the size of the tumor mass was noted during therapy.

At the present time NSC-1026, Oxylone and Hexestrol have been given very limited trials here but will be included in this review for the sake of completeness.

The following patients were treated with NSC-1026:

E.M.: This 56-year old man had a poorly differentiated squamous cell carcinoma the primary site of which was not determined, but which presented as a mass in the left neck for which a radical neck dissection was done. In a short time there was a mass in the left shoulder and the drug was begun. During therapy no toxic reactions were recorded but the mass increased by about three centimeters in all dimensions. More metastatic masses were to develop and the therapy was categorized as ineffective.

I.J.: This 64-year old man had a squamous cell carcinoma of the esophagus and told of mild dysphagia beginning some three months before the diagnosis was made. At the time he presented at this hospital, his symptoms were moderately severe and metastases were noted in the right supraclavicular region. During therapy moderate anorexia was encountered but was not so severe as to necessitate discontinuance of the drug. During therapy the size of the metastatic nodules remained unchanged and the patient's course was progressively downhill with death occurring in about two months following use of the drug.

M.B.: This 46-year old woman had a primary adenocarcinoma of the ascending colon for which a right

colectomy was done about three years before being entered on the CDE program. Also in this three-year period, obstructive symptoms had occurred from local growth and a cholecystojejunostomy and a gastrojejunostomy were done. About two years before NSC-1026 therapy the patient was given a full course of 5 F.U. without result. Numerous transfusions had to be given for G.I. bleeding. The course of NSC-1026 was given without complications and during therapy the epigastric mass which was being used as a measure of effectiveness decreased greatly in size. Some relief of symptoms was obtained but following the drug more problems from the widespread disease were to develop. It was felt that a response to the drug was in evidence.

Summary: This drug was given to but three patients and toxicity of a mild degree was observed in one. In the other patient no effects toxic or therapeutic were observed. In the third patient who had long-standing extensive disease, a good response was obtained without the disadvantage of toxicity.

The following patients were treated with Oxylone:

E.L.: This 59-year old man had a primary adeno-

carcinoma of the right lung with metastases to the brain as demonstrated by biopsy. He gave a history of dizziness and falling of about twelve years duration and at the time he was seen here he had many left-sided findings. Seven weeks of therapy was given without problems and the full course was cut short by the death of the patient who had had no response.

C.K.: This man had an adenocarcinoma of the stomach with distant metastases. A full course of the drug was given without complications but it was felt that no response was obtained as there was no decrease in the size of the lesions and the G.I. symptoms he was having continued unchanged.

Summary: Both of the patients treated with this drug tolerated it well but neither showed even a slight response to treatment.

The following patient was treated with Hexestrol:

G.D.: This 61-year old man had an adenocarcinoma of the right kidney with metastatic masses in the right lumbar and right flank areas. A full course of the drug was given without problems and the metastatic areas continued to enlarge. Response was negligible.

SUMMARY

The Clinical Drug Evaluation Program has been in operation at University Hospital for about four years at the present time. Drs. Musselman and Miller were the first to take charge of the program here and have continued in that role with the addition of the services of Dr. Westfall. As noted, there are rather strict criteria as to patient selection and some difficulty has been encountered in obtaining a sufficient quantity of cases which are suitable for entry into the program; however, by adding patients from all participating institutions, sizeable samplings can be obtained.

So far at this hospital, alanine mustard, methotrexate, hexamethylmelamine, NSC-1026, oxylone and hexestrol have been used, although as noted some have had a very limited trial. Some of the properties of these drugs are found in preceding pages and need not be reviewed here. It can be noted that in certain of the drugs the mechanism of action is known, whereas in others it is a complete mystery.

The patients treated thus far have been categorized as to the drug used and all patients upon whom

all data are complete were presented, although there have been others recently whose cases are not yet in the permanent files here. It is to be remembered that all patients who are placed on this program have far advanced disease and are beyond the help of other anti-cancer methods. After each series of patients, a brief summary of the experience with each particular drug is given and need not be repeated in this final summary.

The treatment of mitotic disease in its far advanced stages is oftentimes futile, but if any degree of comfort is given in the remaining months, treatment is certainly justified. Another factor which I believe is important is that the terminal patient can feel that something is being done and he or she has not been left to die without any further aid. It can be argued that the patients who have severe reactions to the drug make this attempt meaningless. In the patients who became toxic, the symptoms usually subsided when the drug was discontinued or shortly thereafter. The moral obligations and implications are not well delineated but, from the medical standpoint, so long as there is any hope of benefit treatment must be given.

ACKNOWLEDGEMENTS

I would like to take this means of thanking Dr. Daniel Miller for his assistance in organizing the material and for his helpful suggestions as to improvements once the rough draft was completed. A vote of thanks also goes to Mrs. Lois Hermsen who assisted in extracting the necessary materials from the records.