Combination Chemotherapy in Malignant Diseases

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This article attempts to show how the practical application of combination chemotherapy has improved both the quality and duration of life, and what benefit it may bring in the future. The principles behind its use may be summarised as follows:

One of the obvious facts about single anti-cancer agents when used on a continuous basis was that eventually the malignant cells became resistant to the drug, and the treatment had to be changed. By analogy with bacteria it would therefore seem reasonable to use drugs in combination, both to lessen the development of resistance and to produce an enhancing effect. In addition, the fact that resistance to one drug is not accompanied by resistance to another, particularly when they have different modes of action, further supported the concept of the use of combination chemotherapy.

The amount of any anti-tumour agent that can be given depends on the toxicity of the drug. Virtually all chemotherapeutic agents exert some depressing effect on the bone marrow, but the degree of depression varies considerably from drug to drug. In addition, each agent may have its own specific adverse effects which preclude more of that drug being given but do not prevent another being used. For example, the amount of vincristine that can be administered is limited by its neurotoxicity and not by its effect on the marrow. It can, therefore, be used quite readily with an alkylating agent such as nitrogen mustard, which is not neurotoxic but has more effect on the marrow. In this way one can obtain a greater anti-tumour effect without increased toxicity.

All regimes of combination chemotherapy incorporate the idea of intermittent treatment, the principle behind which is that the combination of drugs will attack all dividing cells, both normal and malignant. However, a period without treatment between the courses of combination chemotherapy will allow the normal cells of the bone marrow and gastro-intestinal tract to recover before the next course is given, which enables more of the effective agents to be used without increasing the toxicity.

It is proposed to illustrate the use of combination chemotherapy by reference

to acute leukaemia and Hodgkin's disease, in which it is now an established practice, and to discuss its possible role in other forms of malignant disease.

ACUTE LYMPHOBLASTIC LEUKAEMIA

Until recently, the generally accepted regime for treating malignant diseases such as acute leukaemia and the lymphomas was to give one chemotherapeutic agent continuously until it failed to have any effect because of acquired resistance, and then to try another. The aim throughout was to prolong useful active life, but the idea of curing a patient by this means was not envisaged.

There are now at least nine drugs known to be effective in acute leukaemia: prednisone, vincristine, cytosine arabinoside, rubidomycin, asparaginase,

TABLE 1. Intensive Treatment Schedules for Acute Lymphoblastic Leukaemia Carried Out at the National Cancer Institute, Bethesda

VAMP
5 courses each lasting 10 days were given during remission consiting of:

Vincristine	2 mg/M²/week (2 injections per course)
Methotrexate	20 mg/M² every four days I.V.
6-Mercaptopurine	60 mg/M²/day by month
Prednisone	40 mg/M²/day by month

POMP
5 courses each consisting of:

Vincristine	2 mg/M²/week I.V. (2 injections per course)
Methotrexate	7·5 mg/M²/day I.V. for 5 days
6-Mercaptopurine	600 mg/M²/day I.V. for 5 days
Prednisolone	1,000 mg/M²/day I.V. for 5 days

After five courses have been given courses are repeated monthly for twelve months

BIKE
First Course (remission induction):

Prednisone	40 mg/M²/day by mouth
Vincristine	2 mg/M²/week I.V.

Second Course:

Methotrexate	15 mg/M²/day I.V. for 5 days

Third Course:

6-Mercaptopurine	1,000 mg/M²/day I.V. for 5 days

Fourth Course:

Cyclophosphamide 1,000 mg/M² I.V.—single dose
The second and fourth courses were then repeated

cyclophosphamide, 6-mercaptopurine, methotrexate, and BCNU. It is easy to see from this that the possible combinations and permutations are considerable, but the three best-established regimes, which originated in the USA and are known as VAMP, POMP and BIKE (Table 1), all involve

different ways of giving at least four agents—vincristine, prednisone, 6-mercaptopurine, and methotrexate. Using these regimes 50 per cent of children with acute lymphoblastic leukaemia survive more than three years, compared with only five months in the days before specific chemotherapy was available (Freireich *et al.*, 1965; Henderson, 1967).

One of the principles that emerged from the treatment of acute leukaemia was that some drugs were better used when there was obvious active disease (i.e. to induce remission), while others appeared more effective in controlling the disease once the number of malignant cells had been greatly reduced (a period now referred to as 'consolidation' or 'cyto-reduction'). Figure 1 shows the effect of single drugs compared with combinations in inducing remissions in the acute lymphoblastic leukaemia of children; the best combination shown here being vincristine and prednisone, which produced complete remission in 84 per cent of the patients. This is now the standard treat-

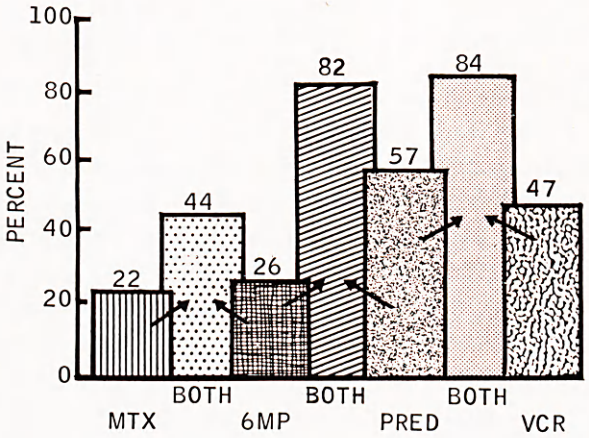

Fig. 1. Effect of single drugs and of combinations (shown in adjacent pairs) in inducing remissions in acute lymphoblastic leukaemia in children. (Reproduced from an article by Holland (1968) by kind permission of the publishers.)

ment for inducing remissions in acute lymphoblastic leukaemia, and some would now claim over 90 per cent of complete remissions with these two drugs. Once complete remission has been achieved, other agents are used for consolidation and maintenance, as shown in Fig. 2.

Because of the large number of possible combinations of drugs, many centres use different treatments in an uncontrolled manner, and in insufficient numbers of patients to make analysis of the results possible. For this reason in

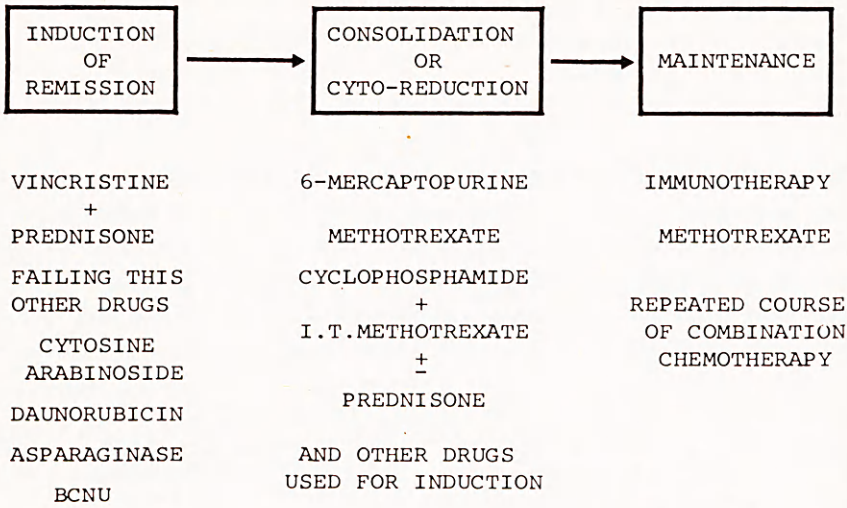

Fig. 2. Scheme for the treatment of acute lymphoblastic leukaemia.

many countries large-scale trials are organised (in Britain by the Medical Research Council) to compare different regimes, and it is essential that as many centres as possible should collaborate in such trials, which have already proved to be of great value. For example, Holland (1969), reporting on the work of the Acute Leukaemia Group B in the USA, has shown that after induction of remission, followed by various regimes of consolidation, a very effective form of maintenance treatment is methotrexate given twice weekly by mouth. Mathé (1969) has also achieved long-maintained remissions following intensive chemotherapy by using immunotherapy with non-specific stimulation with BCG, and/or specific immunisation with irradiated leukaemic cells.

There is another reason why the treatment of acute lymphoblastic leukaemia should be based on centres with special knowledge and facilities. The complications of the disease, particularly the occurrence of a haemorrhagic state due to thrombocytopenia and infections due to neutropenia, have been accentuated due to the use of intensive combination chemotherapy. Indeed, it is highly undesirable that such chemotherapy should be given unless facilities for platelet transfusions and nursing in a sterile environment are available. This does not mean that patients have to be treated in such centres all the time, but that their treatment should be planned by such a centre and the facilities used for those periods during the disease when they are required (James *et al.*, 1967; Fairley, 1969).

If a remission is not obtained with the combination of vincristine and prednisolone, the other drugs listed in Fig. 2 should be used, and if these fail, the compounds normally reserved for the consolidation period should be tried. When a patient in remission relapses, vincristine and prednisolone should be used again, and often another remission is obtained. Failing this, the other drugs should be used.

Quite deliberately, no attempt has been made to give a specific regime for the treatment of acute lymphoblastic leukaemia, because the detail changes so rapidly. However, the principles are unlikely to alter greatly in the immediate future and are worth reiterating:

1. The treatment should be planned in collaboration with a special centre whose facilities may be required at a time when intensive chemotherapy is used.

2. The essential initial aim is to produce a remission. This should be followed by further intensive combination chemotherapy to reduce the number of malignant cells as far as possible.

3. Some form of maintenance treatment should follow this, as shown in Fig. 2.

In the United Kingdom the Medical Research Council has a controlled trial for the treatment of acute lymphoblastic leukaemia, and the more cases admitted to this study the quicker we will be able to determine the best forms of treatment.

ACUTE MYELOBLASTIC LEUKAEMIA

Until very recently, treatment for this form of leukaemia was most disappointing, and there was even a controversy between Crosby (1968) and Boggs *et al.* (1969) about whether myeloblastic leukaemia should be treated at all. However, the introduction of the newer drugs such as cytosine arabinoside and daunorubicin have changed the attitude to treatment, although the prognosis is still much worse than in acute lymphoblastic leukaemia.

It is clearly logical to apply the principles already discussed for lymphoblastic leukaemia to the treatment of myeloblastic leukaemia, although the individual drugs used may differ. For example, vincristine and prednisone, which are so effective in acute lymphoblastic leukaemia, are less effective than daunorubicin and cytosine arabinoside in acute myeloblastic leukaemia. As with lymphoblastic leukaemia, if a remission is not obtained other drugs must be used.

The position in acute myeloblastic leukaemia is not as clear as in acute

lymphoblastic leukaemia. At St Bartholomew's Hospital we have recently been using a combination of cytosine arabinoside and daunorubicin, and have produced complete remission in 60 per cent of adults with this disease (Crowther *et al.*, 1970). Freireich *et al.* (1970) reported similar results, using a combination of cyclophosphamide, vincristine, cytosine arabinoside, and prednisone. Figure 3 shows a scheme for the use of drugs in acute myelo-

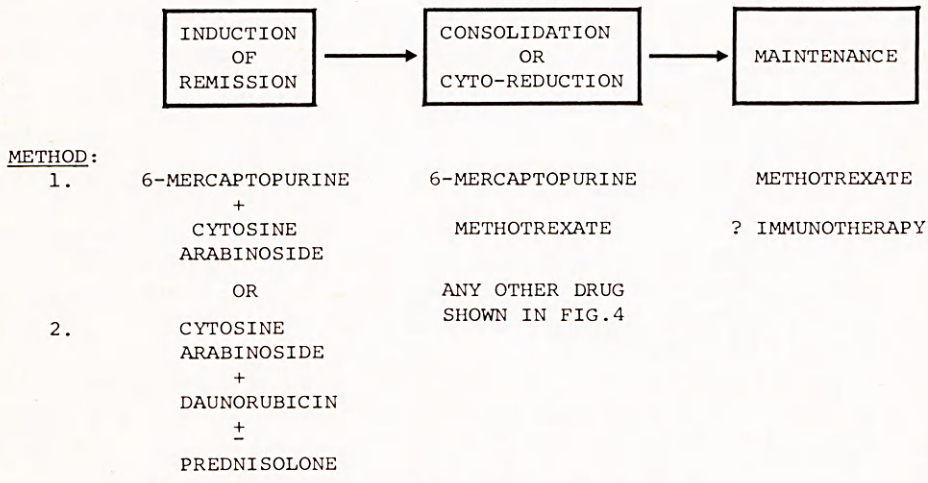

Fig. 3. Scheme for the treatment of acute myeloblastic leukaemia.

blastic leukaemia, and further studies are required to determine which combinations are likely to be most effective. For example, the place of asparaginase is uncertain. It readily clears blast cells from the blood without materially affecting the marrow, so it may have a role if used in combination with other agents (Beard *et al.*, 1970).

In the past, there have been many who have been critical of subjecting patients to intensive combination chemotherapy with all its accompanying toxicity in what is regarded as an inevitably fatal disease. However, an aggressive approach to the treatment of acute leukaemia is justified by the results of Burchenal (1968), who has collected from the entire world 157 cases of proven acute leukaemia of all types, 103 of which are alive and free from disease between five and seventeen years later.

HODGKIN'S DISEASE

If combination chemotherapy is the best form of treatment for acute leukaemia, one might expect it to be effective in other malignant diseases as well, and this is indeed so. In generalised Hodgkin's disease the effective single agents

such as chlorambucil, cyclophosphamide, procarbazine, and vinblastine produce definite improvement in about 70 per cent of the patients (Fairley *et al.*, 1966). However, Carbone (1967), using four agents simultaneously (vincristine, nitrogen mustard, procarbazine and prednisone), produced improvement in 90 per cent of the patients with generalised disease, and in 80 per cent there was complete remission.

The regime we have used at St Bartholomew's Hospital differs slightly in detail, but not in principle, from the one used at the National Institutes of Health (Carbone, 1967) and in Paris by Bernard *et al.* (1967). Their regime consists of six courses, each lasting two weeks, with two weeks rest between each course:

*Prednisone 40 mg/m² daily by mouth
Days 0–14 inclusive
Procarbazine 100 mg/m² daily by mouth
Days 0–14 inclusive
Vincristine 1·4 mg/m²
Days 0 and 7
Mustine hydrochloride 6 mg/m²
Days 0 and 7

(*only given with the 1st and 4th courses)

We have made three modifications. First, we have not used such a big dose of prednisone, because on this dose two patients became psychotic, but we have given our reduced dose with every course. Secondly, we have used vinblastine rather than vincristine because vinblastine is known to be very effective when used as a single agent in Hodgkin's disease, and is less neurotoxic than vincristine. Thirdly, we have lengthened the time interval between courses from two to four weeks. Our regime is as follows:

Prednisolone 40 mg (for an adult patient) daily by mouth
Days 0–14 inclusive
Procarbazine 100 mg/m² daily by mouth
Days 0–14 inclusive
Vinblastine 10 mg (for an adult patient) intravenously
Days 0, 7 and 14
Mustine hydrochloride 6 mg/m²
Days 0 and 7

The results in 52 patients have been reported (Nicholson *et al.*, 1970) and are summarised in Table 2.

TABLE 2. Response to Combination Chemotherapy in Hodgkin's Disease

Group	Number of cases	Number achieving complete remission at some time in their treatment	Response at the time of analysis 2-21 months after starting chemotherapy		
			Complete remission	Partial remission	Failure
No previous treatment	7	6 (86%)	5 (71%)	1	1
Only radiotherapy in the past	19	15 (79%)	12 (63%)	5	2
Chemotherapy ± radiotherapy in the past	26	9 (35%)	5 (19%)	11	10
Total	52	30	22	17	13

There are two essential aims in using chemotherapy in disseminated Hodgkin's disease: to produce complete (or, failing this, partial) remissions and to maintain these remissions for as long as possible. De Vita *et al.* (1969) have shown that, after complete remissions have been obtained with six courses of combination chemotherapy, relapses occur if no further treatment is given. Therefore, it is now our policy to give six courses of treatment, leaving four weeks between each course. If at the end of this time there are still signs of disease, further courses are given, preferably at monthly intervals; or, if the patients are completely unresponsive, other agents such as BCNU or bleomycin are used. Patients who are in complete remission after their first six courses are then given courses at three-monthly intervals for one year, and four-monthly intervals for the next year.

In general, patients have tolerated this form of combination chemotherapy extremely well, and no patient has refused to have a further course. There are several reasons for this: the relief of symptoms is very rapid, probably due to intravenous nitrogen mustard on the first day of treatment. The toxic effects have been less than anticipated, and are exactly what one would expect. Injection of mustine hydrochloride causes nausea and vomiting unless preceded by chlorpromazine, and for this reason the patients remain in hospital for the night following the injection. Nausea and vomiting occasionally occur with procarbazine, but are usually readily controlled by oral perphenazine. It is important that the time spent in hospital during each course is short, and the patients have only two overnight admissions in each fourteen-day course (Days 0 and 7). The injection of vinblastine on Day 14 is given as an out-patient. Courses are often arranged at weekends, so that patients can

continue their work uninterrupted. Neurological complications are not seen with the dose of vinblastine used in our regime, although peripheral neuropathy is common if vincristine is used. The features of Cushing's syndrome are negligible when prednisolone is used in this intermittent fashion.

The major toxic effect is on the bone marrow. Severe depression of the white blood count may occur, particularly in patients who have had previous chemotherapy. It is for this reason that we lengthened the time interval between courses from two to four weeks, and in some patients even longer provided they are in remission. Our aim was to give as complete a course as possible at longer intervals, rather than to adhere rigidly to a time schedule and to be forced to give inadequate dosage.

Depression of bone marrow activity was more marked in patients who had previously had chemotherapy, and it proved irreversible in five patients who have died. These patients, however, had had prolonged courses of cyclophosphamide, vinblastine or procarbazine before being treated with combination chemotherapy. Transient episodes of leucopenia and thrombocytopenia have occurred after combination chemotherapy in patients who have never received chemotherapy in the past. These, so far, have always recovered after a variable period of up to eight weeks, and in no patients have we had to stop treatment.

It is essential to keep a close watch on the blood count, haemoglobin, white cell count, and platelets, and this is done on Days 0, 7, and 14 in each course. Doses of drugs given may have to be modified accordingly. It is our experience that anaemia, leucopenia, and thrombocytopenia occur more frequently with the increasing number of courses given. The interval between courses is three months after six courses to prevent undue bone marrow depression.

As with acute leukaemia, such treatment is best carried out in centres with special facilities for treating thrombocytopenia and leucopenia. The Medical Research Council is undertaking trials of different forms of treatment at the present time.

OTHER MALIGNANT DISEASES

The other lymphomas (lymphosarcoma and reticulum cell sarcoma) also respond to combination chemotherapy, but it is still not firmly established that combinations are superior to single agents in maintaining the remissions. Most of the other carcinomas, such as those of bronchus, stomach, colon, pancreas, and malignant melanoma, are unresponsive to chemotherapy; but occasionally a surprising but gratifying regression may be obtained by using one of the alkylating agents or the newer anti-metabolites such as 5-fluorouracil, particularly when they are used in combination. It is, therefore, worth

while giving at least one course of treatment. Sporadic cases of cancer, including oat cell carcinoma of the bronchus, malignant melanoma, and some adenocarcinomas and teratomas, have been recorded as responding to various combination regimes. An example is shown in Fig. 4.

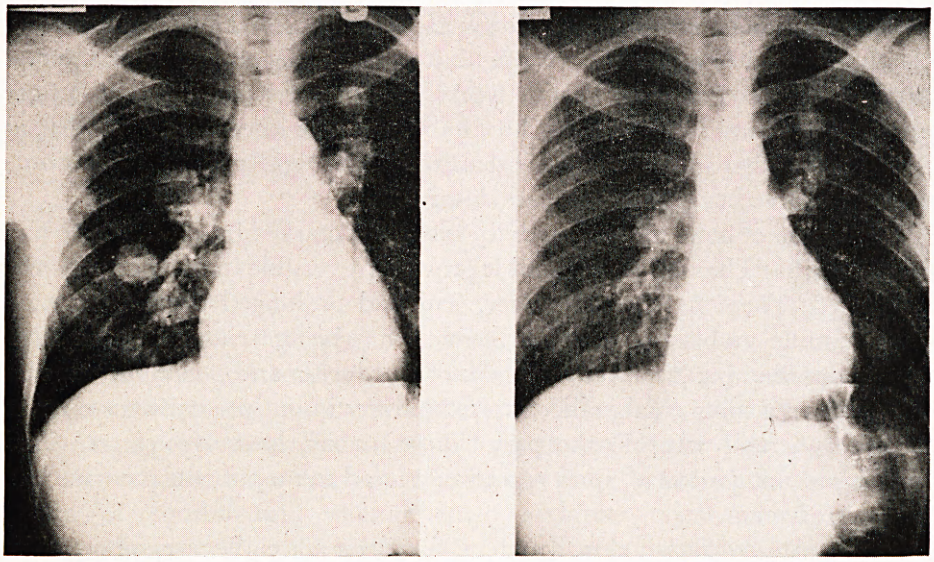

Fig. 4. X-rays taken before and after combination chemotherapy with vincristine, natulan, nitrogen mustard, and prednisone in a man aged 27 with teratoma of the testis, which had failed to respond to all other forms of chemotherapy, showing regression of some of the pulmonary metastases.

Combination chemotherapy clearly represents a considerable advance, which could be expedited by further basic research into the mode of action of the various chemotherapeutic agents to determine the best type of combination and the grouping of patients into special centres so that different forms of treatment can be compared under strictly controlled conditions to give a more rapid appraisal of the different combinations.

Much of this article has deliberately been devoted to the treatment of the reticuloses, for it is here that the drugs are most effective and the best methods of administration can be studied. Applying what has been learned in these diseases to the treatment of other malignant diseases will certainly improve our management of many forms of malignant disease.

This article is based on a paper read at the Conference on the Treatment of Malignant Disease held at the Royal College of Physicians in July 1970.

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The Gossip of J. Cordy Jeaffreson (1861)

The bottle and the board were once the doctor's two favourite companions. More than one eminent physician died in testifying his affection for them. Dr Beddoes was so stout that the Clifton ladies called him their 'walking feather-bed'. Dr Flemyng weighed twenty stone and eleven pounds, till he reduced his weight by abstinence from the delicacies of the table, and by taking a quarter of an ounce of common Castile soap every night. Dr Cheyne's weight was thirty-two stone till he cured himself by persevering in a temperate diet. Laughing at two unwieldy noblemen whose corpulence was the favourite jest of all the wits in the court, Louis XV said to one of them, 'I suppose you take little or no exercise'. 'Your majesty will pardon me,' replied the bulky duke, 'for I generally walk two or three times round my cousin every morning'.

Sir Theodore Mayerne, who, though he was the most eminent physician of his time, did not disdain to write, 'Excellent and Well-approved Receipts in Cookery, with the best way of Preserving', was killed by tavern wine. He died after returning from supper in a Strand hotel; his immediate friends attributing his unexpected death to the quality of the beverage, but others, less charitable, setting it down to the quantity.