Chemotherapy of Hodgkin’s Disease

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The use of chemotherapy to treat lymphomas and, in particular, Hodgkin’s disease has been through three phases in the last 30 years. The first demonstration that chemotherapy was effective in a disseminated malignancy such as advanced Hodgkin’s disease caused excitement and the expectation that at last malignant disease was treatable by drugs. This was succeeded by a sense of frustration when the patients relapsed even after some time in good health. When additional effective drugs were available, the era of drug combination therapy became possible. This form of treatment now offers the chance of cure to a significant number of patients with advanced Hodgkin’s disease.

A fourth phase is now being entered when questions about the most satisfactory and safe combinations of drugs are being asked. The problem of patients who do not respond, or who, having responded once, are in relapse, needs a solution. The once clearly defined indications for the use of radiotherapy and chemotherapy are again becoming blurred and the proposition that they should be combined is being investigated in some centres.

A review of the treatment of Hodgkin’s disease 15 years ago would have indicated that radiotherapy was the treatment of choice and was curative in a large proportion of patients in the early stages of disease. Staging of disease along the lines suggested by Peters and her associates[1] in 1966, and later the Ann Arbor[2] classification in 1971 (Table 1) was accepted. Radiotherapy was used for patients with stage IA, IIA, IIB and IIIA disease. Patients with stage IIIB, IVA and IVB would be treated with drugs. The effective drugs available were nitrogen mustard, chlorambucil, cyclophosphamide, vincristine, vinblastine and procarbazine (Natulan) and the bischloroethyl nitrosourea (BCNU), bleomycin, adriamycin and dimethyl triazeno imidazole carboxamide (DTIC) had not been introduced.

Hamilton Fairley and co-workers[3] reported their experiences with single agents such as cyclophosphamide, vinblastine and procarbazine (Natulan) in patients with disseminated Hodgkin’s disease. They noted responses of the order of 65 per cent and, although they did not use the term complete response, it was probable that they achieved this in about 20 per cent of the patients treated with these three agents (Tables 2, 3 and 4). Similar results were obtained by others[4, 5] using alkylating agents or vinblastine.

The survival of these patients was disappointing, with less than 20 per cent alive at five years (Fig. 1). The survival rate had shown no improvement in the last 30 years. From 1960 onwards the National Cancer Institute

### Table 1. Clinical staging — Ann Arbor[2].

| Stage | Involvement Criteria |
|-------|----------------------|
| I     | Involvement of a single lymph node region (I) or of a single extra-lymphatic organ or site (IE) |
| II    | Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of extra-lymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE) |
| III   | Involvement of lymph node regions on both sides of the diaphragm (III)± involvement of the spleen (IIIS) or localised extra-lymphatic organ or site (IIIE) |
| IV    | Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues, e.g. liver, marrow, pleura, lung, bone and skin |

**Systemic Symptoms — Weight loss, fever, sweating.**

If absent = ‘A’. If present = ‘B’.

### Table 2. Initial results of treatment with cyclophosphamide in 62 patients with Hodgkin’s disease[3].

| Result of Treatment | No. of Patients |
|---------------------|----------------|
| Beneficial          | 43 (69%)       |
| Clinical state unchanged | 6 (10%)     |
| Failed              |               |
| Clinical deterioration | 9 (15%)      |
| Treatment abandoned | 4 (6%)         |

### Table 3. Initial results of treatment with vinblastine in 28 patients with Hodgkin’s disease[3].

| Result of Treatment | No. of Patients |
|---------------------|----------------|
| Beneficial          | 18 (65%)       |
| Clinical state unchanged | 2 (7%)   |
| Failed              |               |
| Clinical deterioration | 4 (14%)      |
| Treatment abandoned | 4 (14%)       |
Table 4. Initial results of treatment with procarbazine in 17 patients with Hodgkin's disease[3].

| Result of Treatment         | No. of Patients |
|-----------------------------|-----------------|
| Beneficial                  | 10 (59%)        |
| Clinical state unchanged    | 2 (12%)         |
| Failed                      |                 |
|    Clinical deterioration   | 2 (12%)         |
|    Treatment abandoned      | 3 (17%)         |

and the Memorial Hospital, New York, independently instituted two combination regimens of drugs. The former institution under the inspiration of David Karnofsky employed four drugs, originally mustine, oncovin, (vincristine), methotrexate and prednisolone. Later, procarbazine was substituted for methotrexate to produce the MOPP regime[6]. Lacher and Durant[7] introduced a two-drug regime, chlorambucil and vincristine, which was superseded. The improvement in response rate was dramatic[8] (Table 5).

Two studies have analysed the factors influencing response to MOPP[6] and to MVPP[9] (where vinblastine was used instead of vincristine). In both studies, patients who had very advanced disease or who had significant amounts of previous chemotherapy did less well. Previous radiotherapy or the type of histology did not affect response rate, and high response rates were seen in patients who had relapsed after previous radiotherapy (Tables 6 and 7).

Table 5. Chemotherapy in Hodgkin's disease[8].

|                        | Percentage of patients with Complete remission (%) | Partial and complete remission (%) |
|------------------------|---------------------------------------------------|-----------------------------------|
| **Single Agents**      |                                                   |                                   |
| No prior treatment     | 26                                                | 71                                |
| Prior treatment        | 3                                                 | 51                                |
| Vinblastine + chlorambucil | 63                                              | 81                                |
| Quadruple therapy      | 80                                                | 90                                |

Table 6. Results of combination chemotherapy-response and status by stage in Hodgkin's disease[6].

| Stage of patients | Induction Complete 1st Remission |
|-------------------|----------------------------------|
|                   | No. of patients failures remissions continuing Deaths |
| IVB               | 31                               | 8*                                               | 23 | 9 | 13* |
| IVA               | 4                                | 0                                                | 4  | 4 | 0   |
| IIIB              | 5                                | 0                                                | 5  | 2 | 0   |
| IIIA              | 3                                | 0                                                | 3  | 2 | 1   |

*Includes both deaths after initial cycle of treatment.

Figure 1. Survival of patients treated with single and multiple drugs. (Malpas, J. S. and Pike, M. (1973) unpublished observations.)
Table 7. Response to combination chemotherapy in Hodgkin's disease[9].

| Group                                      | Total | No. achieving complete remission at some time in their treatment | Response at time of analysis |
|--------------------------------------------|-------|-----------------------------------------------------------------|-------------------------------|
|                                            |       | 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 with or without radiotherapy  | 26    | 9 (35%)                                                        | 5 (19%)                      | 11      | 10      |
| Total                                      | 52    | 30                                                             | 22                            | 17      | 13      |

In subsequent studies, where three, four or five drugs have been used, it appears that the fourth drug is critical. Complete remission rates of only 45 per cent are seen with three drugs compared with 65 to 85 per cent with four or more drugs[10].

It soon became evident that prolonged survival occurred following combination chemotherapy. In an unpublished analysis of MVPP results, Malpas and Pike showed that 76 per cent of patients were alive at five years (see Fig. 1). A more recent analysis[11] showed that this rate of survival is being upheld. Analysis of the survival of 133 patients treated between 1968 and 1972 shows that just as response rate is affected by previous treatment, so survival is much worse in those treated with chemotherapy before being entered into the MVPP programme (Fig. 2).

The loss of a quarter of the patients in the first five years after complete remission was not acceptable, and attempts to prevent relapse and death by maintenance therapy was begun. The question was whether prolonged therapy stopped relapses or whether it was better to give drugs over a period of time, then stop, and if relapse occurred, treat the patient again. For a number of reasons this question has never been satisfactorily answered. In a randomised study comparing 6 courses of MOPP with 6 courses of MOPP and a further 9 courses of maintenance therapy, there was no significant difference in survival in the two groups[12]. Another study[13] came to the same conclusion. These and other studies have had faults in their design—inefficient numbers or bias in randomisation—that have made interpretation difficult.

By the middle of the 1970s the complete remission rates...
in widely differing centres using four-drug chemotherapy were remarkably similar. About 80 per cent of the patients achieved complete response and, of these, some 75 per cent will be alive at the end of five years. This represents a considerable advance, but it still means that at the end of five years only just over half the patients who present with advanced Hodgkin's disease will be alive.

The course of 48 patients with advanced Hodgkin's disease who failed to achieve a response with MVPP therapy and the course of a further 36 patients who relapsed after achieving a response, have been reviewed (Fig. 3)[14]. The median survival for the group failing to respond is only 16 months. The median survival of those who relapse is three years. The attrition in both groups is inexorable, and it seems as if there will be no long-term survivors.

Table 8. Response to alternative therapy in patients relapsing after MVPP remission induction according to regime employed (36 patients).

| Regimen               | Number of times employed | Complete | Partial | Absent |
|-----------------------|--------------------------|----------|---------|--------|
| MVPP                  | 13                       | 7        | 5       | 1      |
| MOPP                  | 18                       | 2        | 9       | 7      |
| CCNU                  | 4                        | —        | 3       | 1      |
| CCNU + Bleomycin      | 8                        | —        | 7       | 1      |
| Bleomycin             | 4                        | —        | 1       | 3      |
| ABVD                  | 3                        | —        | 2       | 1      |
| Chlorambucil          | 6                        | —        | 2       | 4      |
| VM26                  | 1                        | —        | 0       | 1      |
| Miscellaneous         | 3                        | —        | 1       | 2      |
| Total                 | 60                       | 9        | 30      | 21     |

In an attempt to rescue these patients, a variety of alternative regimens have been in use at St Bartholomew's Hospital. A number of drugs were used between 1968 and 1974. The results of these therapies in non-responding and relapsed patients are shown in Tables 8 and 9. It will be seen that there has been a disappointing response rate with all regimens, particularly in those patients who had never responded to MVPP. Bonadonna and his colleagues[15] used adriamycin, bleomycin, vinblastine and DTIC and reported that this regime ABVD showed lack of cross resistance with MOPP. More recently, they have reported a complete response in 62 per cent of patients resistant to MOPP[16]. Our initial experiences were disappointing and in order to examine this question further, all patients who failed to remit or who relapsed from 1974 onwards were treated with ABVD.

The results of therapy in 41 patients, 38 adults and three children, with ABVD have been reported[17]. The protocol for ABVD consists of adriamycin 25 mg/M², bleomycin 10 mg/M², vincristine 1.5 mg/M² (or vinblastine 6 mg/M²) and DTIC 350 mg/M² on days 0 and 14. A 14-day interval was allowed between cycles of therapy.
Table 9. Response to alternative therapy in patients failing to achieve complete remission with MVPP according to regime employed (34 patients).

| Regime             | Number of times employed | Response |
|--------------------|--------------------------|----------|
|                    |                          | Partial | Absent |
| MOPP               | 14                       | 5       | 9      |
| CCNU               | 7                        | 2       | 5      |
| CCNU + Bleomycin   | 13                       | 6       | 7      |
| Bleomycin          | 4                        | 1       | 3      |
| ABVD               | 8                        | 3       | 5      |
| VM26               | 3                        | 0       | 3      |
| Chlorambucil       | 5                        | 3       | 2      |
| Miscellaneous      | 10                       | 2       | 8      |
| Total              | 64                       | 22      | 42     |

Table 10. Response of Hodgkin's disease to ABVD according to response to MVPP[17].

| Response to ABVD | CR | PR | NR |
|------------------|----|----|----|
| CR               | 2  | 1  | 3  |
| PR               | 13 | 10 | 23 |
| NR               | 7  | 4  | 4  |
| Total            | 15 | 41 |

CR: complete remission  PR: partial remission  NR: no response

Hodgkin's disease will be seen. Attempts to improve initial complete response rates can be described under three headings; first, the use of effective agents either to replace components of the basic MOPP regime or the addition of such agents; second, the use of alternating established effective four-drug combinations such as MOPP, MVPP or ABVD, and third, the use of intensive chemotherapy regimes together with radiotherapy.

The South Eastern Cancer Study Group have reported a randomised clinical trial in which BCNU, a nitrosourea, cyclophosphamide, vinblastine, procarbazine and prednisolone have been used to achieve a complete response. The 324 patients were then randomised to receive more of this regime or six cycles of MOPP, or no maintenance therapy[13]. The complete response rate in previously untreated patients was 68 per

Figure 4. Survival from start of ABVD therapy for advanced Hodgkin's disease[17].

The results are shown in Table 10 which compares the response to ABVD with the response to the original MVPP treatment. A complete response was seen in three (7 per cent), a partial response was seen in 23 (56 per cent) and no response in 15 (37 per cent). Seven patients who showed no response to MVPP were also refractory to ABVD. This disappointing result was also reflected in survival from the beginning of ABVD therapy (Fig. 4).

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cent and they were unable to demonstrate any advantage in survival for patients treated with maintenance chemotherapy. Six patients developed BCNU pulmonary toxicity and, of these, five died. This careful study is probably indicative of the problems that will be met with using this approach.

An example of the use of a 'combination of combinations' formula is seen in the Milan group's use of MOPP and ABVD. Preliminary reports indicate a satisfactory increase in the complete response rate and in survival[19] (Tables 11 and 12).

| Table 11. MOPP vs MOPP + ABVD in Stage IV Hodgkin's disease[19]. |
|---------------------------------------------------------------|
|                | MOPP (%) | MOPP + ABVD (%) |
| CR             | 64       | 79              |
| PR             | 12       | 21              |
| CR + PR        | 76       | 100             |

| Table 12. MOPP vs MOPP + ABVD in Stage IV Hodgkin's disease[19]. |
|---------------------------------------------------------------|
| 1st Year | 2nd Year | 3rd Year |
| CR survival | CR survival | CR survival |
| MOPP | 92 | 80 | 80 | 59 |
| MOPP + ABVD | 100 | 93 | 93 | 82 |

The frequency with which relapse occurs at the primary site of disease has suggested that radiotherapy to the initial sites of bulk disease might be effective. Proznits and his associates[20] combined chemotherapy with a low-dose irradiation schedule. Seventy-five per cent of the patients achieved a complete remission, and a relapse-free survival of 90 per cent at three years was reported. The Stanford group have reported a small series of patients with stage IIIB Hodgkin's disease treated with two chemotherapy regimes and a course of total lymphoid irradiation sandwiched between the chemotherapy[21]. Twenty-two of 25 patients achieved a complete response and at two years all those who obtained a complete response are in remission. These results are significantly better than those achieved by historical controls, but the small numbers and the relatively short follow-up must induce a certain amount of caution in their interpretation. A further study shortly to be published from the Memorial-Sloan Kettering group has used an eight-drug MOPP/ABVD chemotherapy programme together with local radiotherapy to the site of bulk disease. Complete response rates of 80 per cent were achieved and the estimated two-year relapse rate for the group achieving complete remission is 9 per cent.

These regimes are undoubtedly toxic and difficult for the patient to tolerate, and the proportion of drugs given to that required by protocol is often only half to three-quarters, which is significant. More disturbing are the recent reports of leukaemia and second tumours occurring in patients treated for Hodgkin's disease.

Leukaemia is seen subsequent to chemotherapy, and solid tumours occur in previously irradiated sites. The use of both these methods of treatment increases the hazard[22].

There may be an alternative explanation why so many treatments are not completely successful. The definition of complete response in Hodgkin's disease is looser than that of complete remission in acute leukaemia because the latter is based on a second examination of the bone marrow. Second biopsy of affected sites in Hodgkin's disease has been a rare procedure. In Hodgkin's disease complete response is based on clinical criteria and is therefore less satisfactory. If this is so, the possibility must arise that some patients who are said to have achieved a complete response have not done so.

Kaplan[23] showed that extended field irradiation could be curative in 80 per cent of patients with early Hodgkin's disease, and posed the question why radiotherapy was unsuccessful in the other 20 per cent (Fig. 5). In most cases this was due to disease appearing outside the irradiated area, particularly in the abdomen. When staging laparotomy was done with biopsy of abdominal lymph nodes and removal of the spleen for histological examination in patients with early stage Hodgkin's disease, the number found to have unsuspected disease in the abdomen matched the proportion expected from Kaplan's study remarkably closely (Table 13)[24].

Figure 5. Survival rate of patients with early Hodgkin's disease after extended field radiation[23].
An analogous situation could exist with chemotherapeutic treatment. To prove the hypothesis it is necessary to be able to recognise the appearance of active Hodgkin's disease and, also, scarred or treated disease. This is possible, as the photomicrographs in Figs 6 and 7 show. Sutcliffe and fellow workers[25] studied 19 patients who had been treated with standard MVPP therapy and who appeared to be cured of their disease. These patients had a post-treatment laparotomy (Table 14). Since publication, a total of 36 patients have had a post-treatment laparotomy. In only five of these, 14 per cent, has unsuspected disease been found, so that the earlier assessment of about 20 per cent is steadily falling with increasing numbers. It appears, therefore, that this incidence of unsuspected disease is not able to explain the loss of 25 per cent at five years. It must be concluded that there are a proportion of cases where a true reappearance of disease occurs. On theoretical grounds, a 100 per cent cure rate for advanced Hodgkin's disease will not be possible, certainly with current therapy.

To summarise the present position in the treatment of advanced Hodgkin's disease, a stage which would be most appropriately treated with chemotherapy, there would be general agreement that patients should not be given single drugs or inadequate or poor combinations of drugs before having definitive multiple drug chemotherapy, as response rates and survival are uniformly poor in pre-treated patients. There would be agreement that an attempt must be made on the first occasion to achieve a complete response. The outlook for patients who do not respond is poor. Most would agree that maintenance programmes are not effective and increase the hazards of leukaemia. The value of post-treatment laparotomy and of its effect on long-term survival is not known, although it has thrown light on the biology of the disease. At present, no multidrug regimens or combination of radiotherapy and chemotherapy have been shown to increase long-term survival compared with standard four-drug combinations. There does appear, instead, to be an increase in the risk of leukaemia and second tumours when they are employed.

This article is based on a paper read at the College Regional Conference in Birmingham in September 1979.

References
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2. Report of the Committee on Hodgkin's Disease Staging Classification (1971) Cancer Research, 31, 1860.
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Table 13. Results of pre-treatment staging laparotomy for Hodgkin's disease above diaphragm[24].

| Clinical Stage | No. of Patients | Same | Pathological Stage Increased | Decreased |
|----------------|----------------|------|-----------------------------|-----------|
| IA             | 23             | 16   | 7                           | 0         |
| IB             | 1              | 0    | 1                           | 0         |
| IIA            | 22             | 14   | 8                           | 0         |
| IIB            | 1              | 3    | 1                           | 0         |
| IIIA           | 18             | 11   | 3                           | 4         |
| Total          | 68             | 44 (64%) | 20 (30%) | 4 (6%)     |

Figure 6. Lymph node biopsy. Active Hodgkin's disease before treatment.

Figure 7. (Same case) Lymph node biopsy at staging laparotomy after treatment. Hyalinisation in areas of former Hodgkin's disease.

Table 14. Histological findings after chemotherapy[11].

| Evidence of abdominal disease | No evidence of abdominal disease | Histological Appearance of Disease Ablated | Partially Ablated | Unmodified |
|------------------------------|---------------------------------|------------------------------------------|-------------------|------------|
| In complete remission        | 19                              | 12                                       | 3                 | 1          | 3          |
| Suspected abdominal disease  | 2                               | 1                                        | 1                 | 1          |            |

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Book Review

The Analysis of Hysteria. Harold Merskey. Bailliere Tindall, 1979. 310 pages. Price £9.50.

Beginning his book with a historical review of the subject, Dr Merskey traces the concept of hysteria from the seventeenth century to the present day. Its chequered history and changing face is well described in summary by Hunter and MacAlpine, who wrote: Though often assailed as aetiological nonsensical, clinically unsound and therapeutically obstructive and gradually whittled away as knowledge of organic neurological disease advanced, hysteria as a diagnostic label has survived’. (From Three Hundred Years of Psychiatry.) The difficulty in a historical review in terms of its relevance to present day medicine is in its relationship to organic disease. In the seventeenth century hysteria had to be distinguished from witchcraft and now towards the end of the twentieth century from, say, the cerebral manifestation of lupus erythematosus. This makes it almost impossible to consider in a relevant way the writings of earlier times simply because what knowledge there was then of neuropathology does not compare with what we know today.

Dr Merskey himself sees that this is so and makes the point in Chapter 13 that ‘blepharospasm, facial dyskinesias, spasmodic torticollis, many tics and even hemichorea’ were classified as hysterical on account of ignorance. Ignorance is ever with us, of course, and today similar mistakes may arise when a collection of neurological or other symptoms does not happen to fit into any pattern the physician recognises.

Dr Merskey believes that ‘hysteria’ is a recognisable psychological illness and that the name should not be discarded. He discusses the clinical guises in which it presents and the problems of treatment and its relationship to other psychological illness. The main text is followed by an appendix in which are reprinted an extract from Landouzy’s book on hysteria, a lecture by Kraepelin on hysterical insanity, a lecture by Sir Charles Symonds on hysteria and lastly a chapter by Hecker on epidemic hysteria as seen in the Middle Ages.

This is an interesting book, full of information, and will be enjoyed by psychiatrists and neurologists as well as by interested general physicians.

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