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# ChlVPP: Reducing Toxicity in the Treatment of Hodgkin's Disease

## Janine L. Mansi

COMBINATION CHEMOTHERAPY for Hodgkin's disease was first introduced at the National Cancer Institute in 1964. This consisted of mustine, vincristine, procarbazine and prednisolone (MOPP). Approximately 80% of patients achieved complete remission with a 5-year relapse-free survival of 68% [1, 2, 3]. Because of these impressive results, MOPP has always been the gold standard on which other treatment regimens for Hodgkin's disease have been based. However, the combination is not without toxicity. The predominant acute toxicity includes nausea, vomiting, superficial thrombophlebitis, peripheral neuropathy, bone marrow suppression and alopecia.

Over the last 20 years various changes have been made to the MOPP regimen in order to reduce the toxicity but without detracting from the clinical efficacy. ChlVPP (Table 1) was first introduced at the Royal Marsden Hospital in 1976 with the aim of avoiding the gastrointestinal toxicity, thrombophlebitis, alopecia and myelosuppression by substituting chlorambucil for mustine, and the peripheral neuropathy by substituting vinblastine for vincristine. Alternative variations along the same line include MVPP (substituting vinblastine for vincristine) [4, 5], LOPP (substituting mustine for chlorambucil) [6], and BCVPP (omitting mustine, substituting vinblastine for vincristine and incorporating carmustine and cyclophosphamide) [7], to name but a few. Early results using ChlVPP suggested

*Table 1. ChlVPP chemotherapy*

| | | |
|---|---|---|
| Chlorambucil | 6 mg/m$^2$ (max. 10 mg) | Orally days 1–14 |
| Procarbazine | 100 mg/m$^2$ (max. 150 mg) | Orally days 1–14 |
| Prednisolone | 40 mg/m$^2$ | Orally days 1–14 |
| Vinblastine | 6 mg/m$^2$ | IV days 1 and 8 |

Cycle repeated every 4 weeks

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*Table 2. Relation of response and survival to various factors*

| | | No. of patients | No CR *n*(%) | Remaining in remission | | Survival | |
|---|---|---|---|---|---|---|---|
| | | | | 5 years (%) | 10 years (%) | 5 years (%) | 10 years (%) |
| Total | | 229 | 194 (85) | 74.4 | 71.3 | 73.1 | 65.2 |
| Sex | Male | 152 | 126 (83) | 72.1 | 67.5 | 84.1 | 73.5 |
| | Female | 77 | 68 (88) | 78.7 | 78.7 | 83.9 | 79.5 |
| Clinical Stage | I | 27 | 26 (96) | 75.2 | 65.8 | 79.3 | 70.5 |
| | II | 89 | 78 (88) | 79.4 | 76.2 | 79.9 | 77.8 |
| | III | 64 | 55 (86) | 68.6 | 66.0 | 71.3 | 58.2 |
| | IV | 49 | 35 (71) | 71.3 | 71.3 | 59.4 | 51.6 |
| B Symptoms | No | 117 | 107 (91) | 76.4 | 72.0 | 80.5 | 73.5 |
| | Yes | 112 | 87 (78) | 71.7 | 69.9 | 65.3 | 56.5 |
| Age | <26 | 74 | 66 (89) | 82.4 | 79.4 | 86.0 | 86.0 |
| | 26–39 | 88 | 71 (81) | 74.3 | 72.3 | 74.6 | 68.0 |
| | 40–59 | 43 | 38 (88) | 61.5 | 61.5 | 66.3 | 39.6 |
| | 60+ | 24 | 19 (79) | 65.7 | 52.6 | 39.7 | 21.7 |

equivalent response rates with less toxicity compared with MOPP and its variants [8, 9, 10].

Fortunately, this combination has also stood the test of time [11]. On completion of the study in 1986, 229 patients had received ChlVPP with a median follow-up of 92 months. No patient had received previous treatment. The median age of the patients was 30 years (range 16–81) of whom 152 were male and 77 female. The histological subtype of the patients was as follows: nodular sclerosis 137, mixed cellularity 70, lymphocyte-predominant 12 and lymphocyte-depleted 10. The majority of patients were stage II (89) or III (64) (Table 2). 'B' symptoms were experienced by 112 patients.

Prior to treatment, all patients were fully assessed by history, physical examination, routine blood tests including liver function tests, chest X-ray, lymphangiogram and bone marrow aspirate and trephine. When clinically indicated, additional evaluation included a CT, liver ultrasound, gallium scan and staging laparotomy. Patients were reassessed prior to each course of treatment by physical examination, chest X-ray, abdominal X-ray and full blood count. On completion of treatment all previously abnormal tests were repeated. A complete remission was defined as return to normal of all previously abnormal clinical findings and investigations.

ChlVPP chemotherapy was given in four weekly cycles. Patients were treated to complete remission plus at least two extra cycles. If the leucocyte or platelet count was less than $3 \times 10^9$/l and $100 \times 10^9$/l, respectively, treatment was delayed by 1 week or until the counts recovered. If grade II neuropathy occurred, the dose of vinblastine was reduced from 6 to 3 mg/m$^2$.

The addition of radiotherapy following completion of chemotherapy was generally, but not always, given to patients with stage I and II disease, and to sites of bulky disease in patients with stage III and IV disease. This was started 6 weeks after the last course of chemotherapy. 53 patients received mantle radiotherapy, 13 patients mantle radiotherapy together with para aortic strip, 8 patients inverted Y, 39 patients total nodal irradiation and 15 patients received modified field radiotherapy.

The complete remission rate was 85% with a 10-year overall survival rate of 76% for those patients who achieved complete remission. This compares with a 10-year survival of only 9.9% for those patients who did enter complete remission. The 10-year relapse-free interval and overall survival for various factors is shown in Table 3. These long-term results are similar to those achieved with MOPP [3] and appear to be better than the recently published results from a randomised study comparing MOPP with LOPP [12].

In general, the treatment was very well tolerated. The toxicity according to WHO criteria is shown in Table 3. Of particular note is the marked absence of nausea, vomiting, alopecia, neuropathy and stomatitis in the majority of patients receiving this combination. Moderate myelosuppression did occur but this was only in a minority of patients. 2 patients died of infection, but they were not leucopenic. Only a small proportion of patients required a dose delay or dose reduction (Table 4). This compares very favourably with other regimens where dose reductions and/or delays are required in over 30–40% of patients [5, 6]. Because the number of patients involved in this series is so small the prognostic significance of this has not been analysed.

Unfortunately, sterility [3, 13, 14] and an increased incidence of second malignancies occur in any combination containing an alkylating agent [15, 16]. Likewise in this study, most male

*Table 3. World Health Organization graded toxicity*

| | Patients (%) | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Anaemia | 20 | 9 | 0 | 0 |
| Leukopenia | 21 | 20 | 7 | 2 |
| Thrombocytopenia | 8 | 10 | 4 | 0.5 |
| Nausea and vomiting | 18 | 13 | 1.5 | 0.5 |
| Alopecia | 5 | 1.5 | 0.5 | 0 |
| Neuropathy | 11 | 3 | 0 | 0 |
| Infection | 8 | 9 | 1.5 | 1.5 |
| Diarrhoea | 2.5 | 0.5 | 0 | 0 |
| Stomatitis | 1.5 | 1 | 0 | 0 |

*Table 4. Dose reduction or delay*

| | Course | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| % of patients with any dosage reduction | 6 | 13 | 13 | 12 | 16 | 15 |
| % of patients with 1 week delay | — | 4 | 7 | 4 | 11 | 5 |
| % of patients with 2 weeks delay | — | 6 | 4 | 6 | 7 | 10 |

patients became (or remained) infertile and the actuarial risk of secondary leukaemia or a second malignancy was 2.7 and 8.3% (this includes five cases of basal cell carcinoma) at 10 years, respectively. New drug combinations are currently being evaluated with the aim of reducing or preventing these long-term toxicities.

In conclusion, ChlVPP combination chemotherapy for Hodgkin's disease represents a major step forward in markedly reducing the acute toxicity seen with other drug combinations whilst maintaining the long-term remissions achieved with MOPP.


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# Expression of Cathepsin D in Head and Neck Cancer

**R. Zeillinger, H. Swoboda, E. Machacek, D. Nekahm, G. Sliutz, W. Knogler, P. Speiser, E. Swoboda and E. Kubista**

**To determine overexpression of cathepsin D in head and neck tumours we examined cytosols from 53 primary tumours, nine cytosols of lymph node metastases and 12 cytosols from adjacent normal tissue. We found a significantly lower concentration in normal tissue compared with tumour cytosol as well as with metastases, even when we compared tumours and corresponding metastases pairwise. In addition, we found a significantly higher concentration of cathepsin D in five lymph node metastases than in the corresponding tumours. We conclude that the reported role of cathepsin D is not restricted to breast cancer but could also be important in head and neck cancer.**

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## INTRODUCTION

CATHEPSIN D, a lysosomal acidic protease [1], possibly degrades extracellular matrix [2] when autoactivated. Thus, it may facilitate dissemination of tumours [3]. It has been reported that cathepsin D is secreted in excess by breast cancer cells compared with normal cells [4]. In clinical studies, overexpression of cathepsin D correlated with aggressive tumour behaviour, early relapse and shortened survival [5, 6]. Compared with histopathological factors, cathepsin D was an independent marker for prognosis, especially in node-negative breast cancer [5–9].