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# CCNU, VINBLASTINE, PROCARBAZINE AND PREDNISONE (CVPP) WITH EXTENDED-FIELD RADIOTHERAPY IN THE TREATMENT OF EARLY UNFAVORABLE HODGKIN'S DISEASE
## A prospective study on behalf of the Gruppo Italiano per lo Studio dei Linfomi (GISL)

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**ABSTRACT**

***Purpose.*** **To test the adequacy of the CVPP four-drug regimen as ancillary chemotherapy associated with extended-field radiotherapy in the treatment of early, unfavorable, clinically staged Hodgkin's disease.**

***Patients and Methods.*** **The population of this prospective, multicenter study consisted of 49 patients with stage I-II disease, associated with bulky involvement or unfavorable histology (lymphocyte-depleted nodular sclerosis or lymphocyte depletion), systemic symptoms or extranodal involvement, or presenting with stage III A favorable-histology disease, with or without extranodal involvement.**

***Results.*** **Complete remission was achieved in 39 patients, partial remission in 2, while 8 patients did not respond. Four patients have relapsed so far (median follow-up: 43 months), all of whom were subsequently rescued with different salvage treatments. Dose intensity (mean±SD: 0.83±0.12) and hematological toxicity (including 2 deaths from infection) were higher when RT followed CT than when it was interposed in the middle of the 6 cycles. No growth factors were used. Non-hematological toxicity was very low and fully tolerable.**

***Conclusions.*** **Results confirmed the mild neurological and gastroenteric side effects of CVPP that make it an interesting MOPP-variant regimen. This combination seems most indicated when a regimen devoid of cardiac and pulmonary toxicity is required for association with full-dosage mediastinal radiotherapy, as is often the case in early, unfavorable Hodgkin's disease. The optimal sequence consists of radiotherapy administered after completion of the chemotherapy program. The use of growth factors for correction (or prevention) of marked leukopenia seems appropriate.**

*Key words: Hodgkin's disease, multiple drug chemotherapy, radiotherapy, early stages, unfavorable prognosis*

Starting in 1988 the GISL treatment policy for Hodgkin patients was differentiated according to three prognostic categories: a) patients with early disease and favorable presentation; b) patients with early disease presenting one or two unfavorable factors; c) cases with advanced disease or very unfavorable presentation.

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At present, combined modality treatment seems to be a reasonable choice for the intermediate-risk group in the opinion of many investigators, as reviewed by Urba and Longo,[1] Straus,[2] DeVita and Hubbard,[3] although various criteria can be utilized to identify patients with early disease and poorer prognosis.

MOPP (mechlorethamine, vincristine, procarbazine, prednisone) chemotherapy, originally designed for advanced stage disease,[4] was also the regimen of choice, together with its many variants, in this subset of patients, who generally received it in combination with radiotherapy.[5-8] A large number of MOPP variant regimens were tested in advanced or relapsed Hodgkin's disease in an attempt to reduce toxicity or improve results,[9] and in the 80's these studies generated some interest for regimens in which a nitrosurea was substituted for nitrogen mustard, either carmustine (BCNU) as in BOPP,[10] BVPP[11] and BCVPP,[12] or lomustine (CCNU) as in CVPP,[13] CEM[14] and LVP.[15]

A MOPP variant using BCNU seemed to offer even better results[12] than MOPP itself, and alternative regimens with CCNU either gave more prolonged remission and lower toxicity as first-line therapy[13] or achieved good remission rates in relapsed patients;[14,15] all of them were easy to administered and well tolerated, resulting in improved patient and physician compliance. These data were confirmed by our Group on a limited series of patients in a preliminary study in which 6 cycles of CVPP (CCNU, vinblastine, procarbazine, prednisone) were matched with the same number of MOPP cycles in both early, unfavorable disease – where they were combined with extended-field radiotherapy – and in advanced disease – where they were alternated with 6 courses of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine).[16]

In 1988 CVPP in combination with extended-field radiotherapy (EFRT) was chosen for a prospective open study on the treatment of early stage, unfavorable Hodgkin patients. The endpoints were a more detailed evaluation of the toxicity and manageability of the regimen, possible confirmation of clinical results comparable to the standards warranted by current combined treatments involving four-drug chemotherapy (MOPP, ABVD), and confirmation of acceptable tolerance by the patients.

### *Materials and Methods*

Between January 1988 and December 1993, 51 patients with early, unfavorable HD were registered for study by 12 GISL member institutions. Patients were required to have biopsy-proven, untreated Hodgkin's disease with the following staging features: stage I-II with bulky involvement ($I_XA$-$II_XA$) or unfavorable histology (lymphocyte-depleted nodular sclerosis or lymphocyte depletion) or systemic symptoms (IB-IIB); stage IA-IIIA with limited extranodal extension ($I_EA$-$III_EA$); stage IIIA with histologic types other than lymphocyte-depleted nodular sclerosis or lymphocyte depletion.

Staging procedures were performed clinically, according to the Cotswolds Meeting criteria.[17] Besides careful physical examination, patients underwent complete hematological and biochemical screening, computed tomographic scan of both chest and abdomen, bone marrow core needle biopsy on one side. For patients with B symptoms a second controlateral bone marrow biopsy and ultrasound-guided liver and spleen needle biopsies were also performed. Lymphangiography was omitted. All the tests performed at initial evaluation were repeated after therapy with the exception of bone marrow biopsy.

Two patients who continued receiving treatment in non GISL centers were lost to follow-up before the end of therapy and had to be excluded from the study. Thus the number of evaluable cases was 49. No restrictions regarding performance status or age were fixed, so the lowest Karnofsky index was 30 and the oldest participant was 79.

The CVPP regimen was scheduled every 4 weeks for a total of 6 cycles and consisted of CCNU 75 mg/m$^2$ given orally on day 1, vinblastine (VBL) 4 mg/m$^2$ injected intravenously on days 1 and 8, procarbazine (PCZ) 100 mg/m$^2$ and prednisone (Pred) 40 mg/m$^2$ administered orally from days 1 to 14. The criteria adopted for dose modification according to toxicity were those indicated by Cooper *et al.*[13] If the leuko-

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cyte count was ≥ $4\times10^9$/L and the platelet count ≥ $100\times10^9$/L, full dosage of CCNU, VBL and PCZ was given. If the leukocyte count was between 3 and $3.999\times10^9$/L or the platelet count was between 75 and $99\times10^9$/L, the doses of CCNU, VBL and PCZ were reduced to 75%. If WBC count fell between 2 and $2.999\times10^9$/L or the platelets were between 50 and $74\times10^9$/L, CCNU, VBL and PCZ doses were reduced to 50%. If the WBC were < $2\times10^9$/L and platelets < $50\times10^9$/L, the drugs were omitted until hematological recovery occurred.

Radiotherapy was administered by megavoltage equipment in 13 different divisions of radiotherapy. The planned irradiation involved subtotal lymphoid irradiation (STLI), including mantle and para-aortic-splenic pedicle fields. In the 6 patients with limited extralymphatic disease (stages $I_E$-$III_E$), the involved extralymphatic organs were included in the irradiated fields. Recommended dosage was 36 Gy (38 Gy on bulky sites of involvement) but unavoidable differences in source, energy, dose fraction, total dose and field extension had to be tolerated from institution to institution.

Complete remission (CR) was defined as complete regression of measured lesions and disappearance of all other objective evidence of lymphoma. Partial remission (PR) was defined as a decrease in measurable lesions to less than 50% of the sum of the products of the diameters of measured lesions. No response (NR) was any reduction less than partial remission.[18] Progression (PG) was judged as an increase of more than 25% in the sum of the products of the diameters of measured lesions and/or the appearance of new lesions.

Dose intensity was calculated for each drug and for the whole regimen according to the criteria reported by Hryniuk[19] and the examples and suggestions furnished by DeVita *et al.*[20]

Toxicity was measured according to standard *Eastern Cooperative Oncology Group* criteria.[21]

Standard techniques of one-way analysis of variance were used to evaluate dose intensity differences.[22] Data regarding toxicity grades were analyzed for possible differences with the Mann-Whitney U test, considering the 0 to 4 grades of toxicity as ranks of observations ordered with increasing magnitude.[22]

Survival was measured from the date of diagnosis to the date of last observation or death. Relapse-free survival (RFS) for complete responders was calculated from the date of therapy completion to the date of last observation or relapse, while failure-free survival (FFS) was measured from the date of start of therapy to the date of disease progression, relapse (after complete or partial remission) or death from any cause. The overall survival and RFS curves were calculated using the method of Kaplan and Meier.[23] Deaths due to causes other than HD or therapy were not censored.

The trial was open and no comparisons among treatments were planned; however, the effectiveness and clinical adequacy of CVPP+EF RT were indirectly checked through a comparison with expected survival according to the prognostic factors present at diagnosis, as recorded in the *International Database on Hodgkin's Disease* (IDHD).[24] The mathematical model of survival of the IDHD, drawn from 5,023 patients treated with protocols used all over the world in the 70's and 80's, was considered a good estimate of the *standard* patient prognosis in relation to the individual clinical characteristics at diagnosis and to the treatment protocols used in recent decades.[25]

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### *Results*

The main clinical characteristics of the 49 study patients are recorded in Table 1. For 34 of them subtotal nodal irradiation was interposed between the third and fourth cycle of CT; in 11 it followed the sixth cycle, while in 4 it was not administered at all, either because of patient refusal or clinical evidence of NR with a consequent shift of the CT regimen. Thirty-nine subjects achieved CR, 2 PR, and 8 did not respond at all.

The mean relative dose intensity of the overall regimen (mean of the doses of the three antiproliferative drugs received during *n* cycles over planned doses, divided by the actual days of administration for the same *n* cycles over planned treatment duration) was 0.86±0.13. In particular, it was 0.92±0.13 in the 15 patients

| | | | | | |
|---|---|---|---|---|---|
| Total no. of patients | | 49 | | | |
| Sex | male | 28 | female | 21 | |
| Age | years mean±SD | 39.4±18.8 | range | 14 - 79 | |
| Performance status (Karnofsky index) median | | 90 | range | 30 - 100 | |
| Stage | | | | | |
| I A | 4 | I B | 1 | III A | 5 |
| $I_E$ A | 2 | II B | 11 | $III_E$ A | 1 |
| II A | 22 | $II_E$ B | 2 | | |
| $II_E$ A | 1 | | | | |
| Histology | | | | | |
| Lymphocyte predominance | 5 | Nodular sclerosis, lymphocyte depletion | | 6 | |
| Nodular sclerosis, undefined | 13 | Mixed cellularity | | 17 | |
| Nodular sclerosis, cellular phase | 7 | Lymphocyte depletion | | 1 | |
| Abdominal or mediastinal bulk | 21/49 | | | | |
| Hb (g/dL, mean±SD) | 12.6±1.7 | range | 10.2-15.1 | | |
| ESR (mm at 1hr, mean±SD) | 48±35 | range | 3-116 | | |
| LDH (mU/mL, mean±SD) | 334±121 | range | 106-667 | | |

Table 1. Clinical characteristics of the patients at diagnosis.

| | *CT-RT (15 pts)* | | | *CT-RT-CT (34 pts)* | | | *Total (49 pts)* | | |
|---|---|---|---|---|---|---|---|---|---|
| Grades | Hb | WBC | Plt | Hb | WBC | Plt | Hb | WBC | Plt |
| 0 | 12 | 10 | 12 | 22 | 7 | 15 | 34 | 24 | 27 |
| 1 | 1 | 2 | 1 | 4 | 9 | 6 | 5 | 11 | 7 |
| 2 | 2 | 2 | 1 | 4 | 8 | 7 | 6 | 10 | 8 |
| 3 | 0 | 1 | 1 | 4 | 5 | 4 | 4 | 6 | 5 |
| 4 | 0 | 0 | 0 | 0 | 5 | 2 | 0 | 5 | 2 |
| *P* | | | *0.251* | | | *0.003* | | | *0.026* |

Table 2. Hematological toxicity (ECOG grades) recorded during administration of CVPP chemotherapy (Mann-Whitney U test).

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with the treatment sequence CT (+RT), and 0.83±0.12 in those treated with the sandwich combination. This difference is statistically significant ($p = 0.0421$) and closely related to the higher frequency of dose reductions or administration delays recorded during cycles 4 to 6 in those patients who had RT interposed between cycle 3 and 4 with respect to those who received RT after the 6$^{th}$ CT cycle. Figure 1 illustrates this phenomenon through the variation in dose intensity recorded in each cycle for the three antineoplastic drugs. It also shows that the decrease in dose intensity during the last cycles involved mainly CCNU and PCZ, which are the most myelotoxic drugs in this regimen, while VBL was affected very little.

A total of 263 cycles were given, with a mean of 5.4 per patients. Hematological toxicity on the whole was considerable (see Table 2). Two of the 4 patients with grade 3 anemia developed transient hyporegenerative anemia and required transfusion of concentrated erythrocytes; two

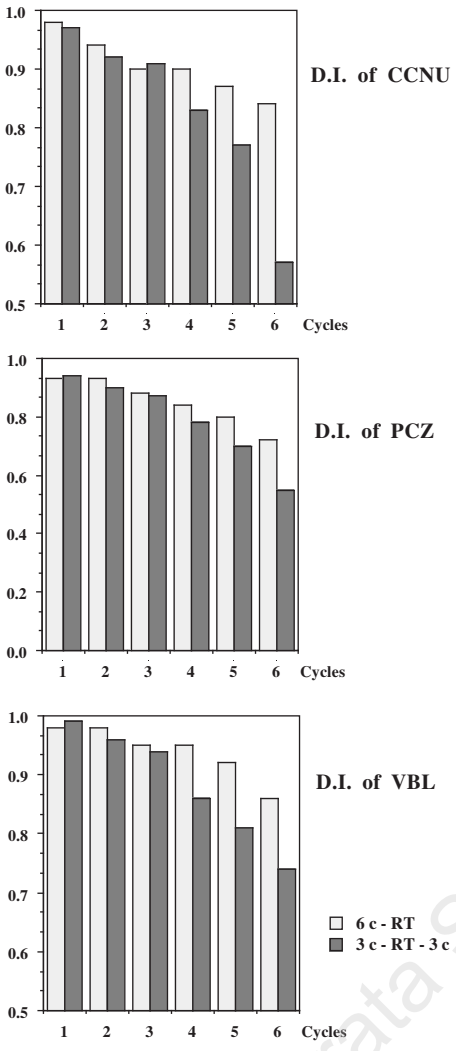


Figure 1. Mean relative single-drug dose intensity recorded for each cycle of the CVPP regimen in the 15 patients who received RT after the 6 CT cycles (or had no RT at all), and in the 34 who received 3 CT cycles before RT and 3 more after it. Reduction in drug dose intensity in cycles 4 to 6 is more evident in patients treated with the sandwich technique.

others recorded grade 4 thrombocytopenia for a few days without bleeding; 5 patients presented grade 3 leukopenia (WBC < $1.999\times10^9$/L) and 5 grade 4 (WBC < $1.00\times10^9$/L). In 6 cases these episodes were febrile and were successfully treated with antibiotic therapy, without the administration of growth factors. On the whole, the hematological toxicity of CVPP was higher when RT was interposed in the middle of the regimen than when it was administered at the end of it. In 8 of the patients treated with the sandwich combination, drug delivery was stopped at the fourth or fifth cycle because of heavy and persistent leukopenia and/or thrombocytopenia. Differences in toxicity grades recorded in the two treatment combinations were statistically significant for both leukopenia and thrombocytopenia, and patients generally tended to complain of stronger hematological toxicity when the $4^{th}$-$6^{th}$ CT cycles were administered after RT rather than before it.

Table 3 shows that nausea, vomiting, hair loss and toxicity to both peripheral and autonomic nerves were present but fully tolerable and had no relationship to the timing of RT. One patient suffered a loss of tendon reflexes with weakness and difficulty in walking, while another complained for a few days of obstipation and failure to pass gas and showed abdominal distension.

Table 4 lists the less frequent side effects and complications, together with the number of patients who refused to continue therapy. Bacterial and viral infections were clinically the most serious or troublesome. Therapy was stopped by patient request after 3 cycles in 1 case and after 4 cycles in another.

RT was administered in 45 patients; 3 subjects did not respond after the first 3 cycles and were admitted directly to salvage chemotherapy, while 1 refused RT after completion of the 6 CT cycles. RT was limited to mantle field in 18 cases, and consisted of STNI in the remaining 27. Patients were given RT with existing supervoltage equipment in 13 different radiotherapy units. Dose fractions varied from 0.17 to 0.22 Gy and total doses ranged from 30 to 47 Gy (median 38.8). Early toxicity from RT was recorded as mild myelosuppression in 3 patients and as transient cutaneous alterations in 6. One patient developed moderately severe postradiation effusive pericarditis but recovered without pericardiocentesis.

Median follow-up is 52 months from the start of therapy (range 14-83) and 43 months from the end of it. Observed overall survival is illustrated in Figure 2, together with the survival expected in the same group of patients according to individual clinical pre-treatment characteristics on the basis of the IDHD mathematical

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| | *CT - RT (15 pts.)* | | | | *CT - RT - CT (34 pts)* | | | | *Total (49 pts)* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Grades | N/V | pNT | vNT | H | N/V | pNT | vNT | H | N/V | pVT | vNT | H |
| 0 | 10 | 14 | 14 | 12 | 16 | 28 | 30 | 25 | 26 | 42 | 44 | 37 |
| 1 | 2 | 1 | 1 | 1 | 6 | 2 | 1 | 2 | 8 | 3 | 2 | 3 |
| 2 | 3 | 0 | 0 | 2 | 11 | 3 | 2 | 6 | 14 | 3 | 2 | 8 |
| 3 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Table 3. Main non hematological toxicity (ECOG grades) recorded during administration of CVPP chemotherapy (Mann-Whitney U test).
N/V= nausea and/or vomiting;
pNT (peripheral neurotoxicity) = paresthesia, decreased tendon reflexes, motor loss;
vNT (visceral neurotoxicity) = constipation to paralytic ileus;
H = hair loss.

*P*
|---------- *0.185*----------|
|---------- *0.302*----------|
|---------- *0.548*----------|
|---------- *0.582*----------|

prognostic model (the figure reports the 67% confidence band given by the expected mean ± 1 standard deviation). It is clear that observed survival falls in the middle of the expected band – and even in its upper half after the fourth or fifth year – thus demonstrating that combined CVPP chemotherapy and EF RT give at least *standard* results according to the clinical experience of the last 25 years and in relation to prognostic factors at diagnosis. Moreover, a trend toward an apparent survival *plateau* can be observed after 40 months.

Table 4. Less frequent side effects or complications related to CVPP chemotherapy.

| | *CT-RT (15 pts.)* | *CT-RT-CT (34 pts)* | *Total (49 pts)* |
|---|---|---|---|
| Meningitis | 1 | 1 | 2 |
| Bacterial pneumonitis | 0 | 2 | 2 |
| H. zoster | 0 | 5 | 5 |
| Viral hepatitis (fatal) | 1 | 0 | 0 |
| Grade-2 toxic hepatitis | 0 | 1 | 1 |
| Hyporegenerative anemia | 0 | 2 | 2 |
| Epigastric pain due to PCZ | 1 | 1 | 2 |
| Refusal to continue CT | 0 | 2 | 2 |
| Refusal to undergo RT | 1 | 0 | 1 |

Figure 3 shows the failure-free survival curve of the whole patient population and the relapse-free survival curve of those 39 who achieved complete remission. No response or disease progression during chemotherapy was recorded in 8 cases, 2 of whom were rescued by salvage therapies, while 6 died with evidence of disease. In all, 7 deaths and 4 relapses have been observed in the whole population so far. The main characteristics of these clinical failures are reported in Table 5. One patient, a 51-year-old female with stage I A disease, lymphocyte-depleted nodular sclerosis histologic type, died of meningitis caused by *Escherichia coli* without evidence of disease after the fourth cycle of CT when her neutrophil count fell to $0.2\times10^9$/L. A second patient, a 68-year-old male with stage $III_X$ A disease, mixed-cellularity histology, died of a hepato-renal syndrome complicating long-standing postnecrotic cirrhosis, 10 months after the end of therapy; the liver disease had hampered correct administration of the CT regimen, to which the lymphoma responded only partially. Another male patient, 34 years old with stage II A disease, mixed cellularity histologic type, who showed a partial remission to CVPP was rescued with 6 cycles of a 9-drug hybrid CT (MOPPEB-VCAD) but died of hepatitis C virus without evidence of disease a few months after completing therapy. An elderly female, aged 79, who had been diabetic since her 60's and suffering more recently from atrial fibrillation, died suddenly of

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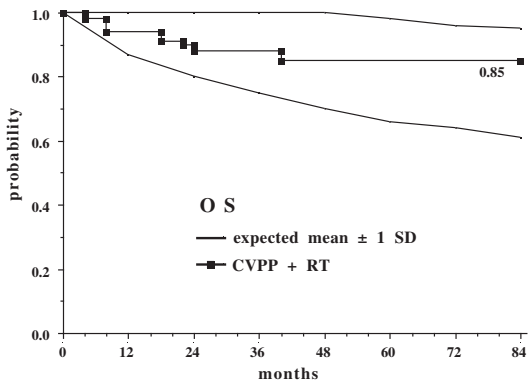


Figure 2. Observed overall survival of the 49 study patients compared with expected survival on the basis of individual clinical staging determinants computed according to the IDHD prognostic model.

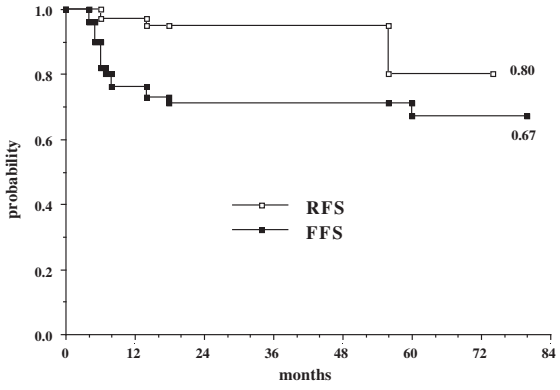


Figure 3. Failure-free survival of the whole population treated with combined CVPP + RT and relapse-free survival of the 39 patients who achieved complete remission.

probable cardiac causes after the third CT cycle, when she was partially responding to therapy. The remaining 3 deaths occurred from disease progression in patients who had not responded either to first-line or to salvage therapy.

There are no apparent common causes or possible explanations for these failures. Three patients (cases 3, 5 and 8) received underdosages of the regimen, mainly due to concomitant pathologies. In all but 3 patients (cases 2, 6 and 9) age was rather advanced. Those patients who did not respond at all to the first few cycles of CVPP also failed with salvage CT, whereas all the ones who relapsed were rescued with MOPP (mechlorethamine, vincristine, procarbazine and prednisone) or alternating MOPP/ABVD (MOPP/adriamycin, bleomycin, vinblastine and decarbazine) or hybrid MOPPEBVCAD CT.

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Table 5. Clinical characteristics of the patients who died of any cause or relapsed.

| | Sex | Age | Stage | Histology | No. of cycles | CT DI | RT Fields (Gy) | Response | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 51 | I A | NS | 4 | 1.00 | not done | CR | Died of meningitis |
| 2 | M | 34 | II A | MC | 6 | .87 | not done | PR* | Died of hepatitis in CR |
| 3 | M | 68 | $III_XA$ | MC | 3 | .73 | STLI (36) | PR | Died of cirrhosis |
| 4 | F | 79 | II A | NS | 3 | 1.04 | not done | PR | Died suddenly # |
| 5 | F | 74 | $II_XA$ | NS (LD) | 3 | .78 | not done | NR | Died in PG |
| 6 | M | 28 | $II_XA$ | LD | 3 | .89 | Mantle (38) | NR | Died in PG |
| 7 | M | 53 | II B | NS (LD) | 3 | .86 | STLI (40) | NR | Died in PG |
| 8 | M | 60 | $II_XA$ | MC | 6 | .75 | Mantle (42) | CR | Relapsed at 6 mo. |
| 9 | M | 23 | I A | MC | 6 | .92 | Mantle (40) | CR | Relapsed at 14 mo. § |
| 10 | M | 57 | $II_XA$ | MC | 6 | .86 | Mantle (36) | CR | Relapsed at 18 mo. § |
| 11 | M | 65 | $II_XA$ | LP | 6 | .80 | Mantle (36) | CR | Relapsed at 56 mo. |

**PR to CVPP, then rescued to CR by salvage chemotherapy; #sudden death of probable cardiac origin; long-standing diabetes mellitus and chronic atrial fibrillation coexisted; √concomitance of silicosis; §relapses outside the irradiated areas.*

So far, no myelodysplastic syndromes or overt second cancers have been found. Fertility was not specifically studied; nevertheless, it is known to have been preserved in some of these patients. A 29-year-old and a 36-year old man have both fathered children since treatment.

***Discussion***

The 1987 GISL decision to divide HD patients into 3 categories according to different staging characteristics with different therapeutic requirements was based on the identification of an intermediate-risk group between patients with early disease and favorable presentation, who could be treated with RT alone or combined with a low-toxicity CT regimen, and those with advanced disease, who require a CT regimen with 7 or 8 drugs – or even more – possibly followed by very limited RT on sites of major involvement.

The allocation of early disease patients presenting bulky involvement or unfavorable histologic type or B symptoms or localized extranodal involvement to this intermediated-risk group proved to be a reasonable choice on clinical grounds. The IDHD prognostic estimation criteria, drawn from a very large international population of patients who received standard staging and treatment in the 70's and 80's, now demonstrate that this group of patients with early disease and unfavorable presentation shows a 0.72±0.18 probability of surviving at 10 years, which is indeed intermediate between that of the early and favorable disease group (0.81±0.13) and that of the advanced one (0.60 ±0.20).

While STNI and VBM (vinblastine, bleomycin and methotrexate) CT were considered adequate in the most favorable subset,[26] and the MOPPEBVCAD hybrid was an interesting solution for the worst prognostic group,[27] there was a general consensus that four-drug CT followed by EF RT would be the best approach for the intermediate prognosis patients. However, a high incidence of bulky mediastinal masses that required using large RT fields and additional local boosts advised against associating CT regimens containing bleomycin and adriamycin, which would have increased the risk of pulmonary and cardiac toxicity, respectively. So, after the hypothesis of ABVD or ABVD-like regimens had been discarded because of their potential cardiac and pulmonary side effects, MOPP or MOPP-like CT remained the most effective alternate solution. The definitive choice of CVPP was determined by the following considerations:

a) in the 80's the interminable search for more effective or less toxic (or both) MOPP-derivative regimens seemed to converge on the usefulness of substituting a nitrosurea for nitrogen mustard. Bakemeier *et al.*[12] obtained the same CR rate with MOPP (73%) and BCVPP (BCNU, cyclophosphamide, vinblastine, procarbazine and prednisone), as well as a significantly longer remission duration and overall survival for the patients treated with BCVPP. Cooper *et al.*[13] in an accurate and elegant clinical trial on 566 patients demonstrated that of MOPP and 3 other MOPP-derived regimens – MVPP (vinblastine for vincristine), COPP (CCNU for nitrogen mustard) and CVPP (CCNU for nitrogen mustard and vinblastine for vincristine) – this last was superior in efficacy and reduced toxicity, and that the use of CCNU was the most significant determinant of prolonged remissions;

b) at the same time CCNU was also receiving increasing attention as an effective agent in many multiple drug salvage regimens, such as CVB[28] (CCNU, vinblastine and bleomycin), SCAB[29] (streptozotocin, CCNU, doxorubicin and bleomycin) and LVB[15] (lomustine, vindesine and bleomycin);

c) a favorable prior experience with CVPP was already available to the GISL,[16] one that confirmed the good results, low toxicity and even better patient compliance than with MOPP.

As far as clinical results are concerned, an 80% CR rate with a 10% relapse rate after a nearly 4-year median follow-up, with projected 5-year survival of 85% must be considered good overall results, somewhat better (see Figure 2) than those expected on the basis of individual pretreatment characteristics according to the IDHD mathematical model. In particular, the estimates drawn from the IDHD were based on a pool of

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patients treated with RT alone or with single or bi-agent chemotherapy in 63% of stage I-II cases and in 26% of stage III A cases, while 37% of stage I-II and 74% of stage III A patients were treated with multiple drug chemotherapy (MOPP or ABVD) with or without RT. Therefore we can conclude that early and intermediate results are at least comparable to those achieved with the combination of chemo- and radiotherapy used in recent decades; moreover, the trend toward a higher survival plateau than that of the mean estimates after the fourth year is of some interest in light of the greater frequency of long-lasting remissions claimed to be produced by CVPP chemotherapy.

Gastroenteric toxicity was mild and fully controlled with metoclopramide, alizapride or prochlorperazine, without the need for HT3 antagonists. Neurotoxicity was slight and easily manageable. No pulmonary toxicity was recorded and this strengthens the idea that, even though CCNU is considered potentially toxic to the lungs, this toxicity does not manifest itself at the usual dosages employed for the treatment of lymphomas, nor does the drug significantly enhance the toxicity linked to RT on the mediastinum.

Infectious complications were a relatively major problem (see Table 4). This is in agreement with the observations of Cooper *et al.*,[13] who correlated an increased frequency of infections with the use of vinblastine in patients over 60 years of age. As a matter of fact, 20% of our patients were over 60 and most of the infective episodes actually did involve this group. However, we believe that the prolonged bone marrow depression related to CCNU may also be implicated along with VBL dosage and advanced age. This is reflected by the greater reduction in CCNU dose intensity that became necessary in most of these patients.

We must point out that a higher frequency of hematological toxicity and infectious complications is commonly observed when CT is combined with extended RT. This is particularly evident when the former follows the latter, even if only a part of the CT regimen is delivered after RT, as was the case for the majority of these patients. For this reason the sandwich administration of CVPP, partly before and partly after RT, has to be abandoned in favor of a schedule in which CT is given entirely before RT. It is noteworthy that no use of growth factors was made throughout the trial. We simply reduced the VBL, CCNU and PCZ doses whenever hematologic toxicity became apparent, according to the suggestions of Cooper *et al.*,[13] and adopted oral antibacterial prophylaxis whenever neutrophil counts dropped below $0.5\times10^9$/L (cotrimoxazole or a chinolonic derivative). The present availability of G- or GM-CSF,[30,31] administered either therapeutically or even prophylactically, would easily solve this problem.

The good results achieved and the mild toxicity recorded, whether absolutely low or easily reducible, make the CVPP regimen the MOPP-derivative of choice for those patients in whom heavy mediastinal RT programs or concomitant pulmonary or cardiac diseases would contraindicate the use of bleomycin- and adriamycin-containing regimens. Its delivery before RT, together with strict therapeutical use of growth factors, is recommended.

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