a professional obligation but also derives from its immense contribution to the future of medicine if one looks at the autopsy as a "collected" autopsy experience and not as a single event [23], providing that the quality of autopsy performance is strictly monitored and under constant control.

Franco Rilke
Anatomia Patologica
Istituto Nazionale Tumori
Via G. Venezian, 1
20133 Milano, Italy

1. Center for Disease Control. Autopsy frequency—United States, 1980–1985. *MMWR* 1988, **37**, 191–194.
2. Becker V. Wozu noch Obduktionen? *Dtsch Med Wochenschr* 1986, **111**, 1507–1510.
3. Peacock SJ, Machin D, Duboulay CEH, Kirkham N. The autopsy: a useful tool or an old relic? *J Pathol* 1988, **156**, 9–14.
4. Hasson J, Gross H. The autopsy and quality assessment of medical care. *Am J Med* 1974, **56**, 137–140.
5. Smith C. The autopsy diagnosis. *Hum Pathol* 1986, **17**, 645–647.
6. Woodruff KH. The relevance of autopsy examination. *Hum Pathol* 1982, **13**, 605.
7. Burrows S. The postmortem examination: scientific necessity or folly? *JAMA* 1975, **223**, 441–443.
8. Reid WA. Cost effectiveness of routine postmortem histology. *J Clin Pathol* 1987, **40**, 459–461.
9. Brown HG. Perceptions of the autopsy: views from the lay public and program proposals. *Hum Pathol* 1990, **21**, 154–158.
10. Henson DE. Revisiting the autopsy. *Arch Pathol Lab Med* 1990, **114**, 127–128.
11. Devers KJ. The changing role of the autopsy. A social environmental perspective. *Hum Pathol* 1990, **21**, 145–153.
12. Roberts WC. The autopsy: its decline and a suggestion for its revival. *N Engl J Med* 1978, **299**, 332–338.
13. Anderson RE, Hill RB, Gorstein F. A model for the autopsy-based quality asessment of medical diagnostics. *Hum Pathol* 1990, **21**, 174–181.
14. Angrist A. The role of the forensic pathologist: Sherlock Holmes or medical and social scientist. *JAMA* 1962, **182**, 929–931.
15. Lawler W. The negative coroner's necroscopy: a personal approach and consideration of difficulties. *J Clin Pathol* 1990, **42**, 977–980.
16. Editorial. Mortality statistics without autopsies: wonderland revisited. *Hum Pathol* 1987, **18**, 875–876.
17. Kircher T. The autopsy and vital statistics. *Hum Pathol* 1990, **21**, 166–173.
18. Stevanovic G, Tucakovic G, Dotlic R, Kanjuh V. Correlation of clinical diagnoses with autopsy findings: a retrospective study of 2,145 consecutive autopsies. *Hum Pathol* 1986, **17**, 1225–1230.
19. Silverberg SG. The autopsy and cancer. *Arch Pathol Lab Med* 1984, **108**, 476–478.
20. Stehbens WE. An appraisal of the epidemic rise of coronary heart disease and its decline. *Lancet* 1987, i, 606–610.
21. Goldman L, Sayson R, Robbins S, Cohn LH, Bettmann M, Weisberg M. The value of the autopsy in three medical eras. *N Engl J Med* 1983, **308**, 1000–1005.
22. Gambino SR. The autopsy. The ultimate audit. *Arch Pathol Lab Med* 1984, **108**, 444–445.
23. Hill RB. The autopsy: a professional obligation dissected. *Hum Pathol* 1990, **21**, 127.

Eur J Cancer, Vol. 27, No. 5, pp. 530–531, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Salvage Treatments in Hodgkin's Disease

DURING THE past 25 years, carefully planned strategies based on natural history as well as on cytotoxic potential of radiotherapy and chemotherapy have dramatically changed the prognosis of Hodgkin's disease from an almost invariably fatal to a highly curable malignancy. In fact, approximately 75% of all patients with this type of lymphoma can now be offered the chance of cure [1, 2]. The impact of various treatments on the 5-year to the 20-year results is now being balanced against delayed morbidity, such as organ damage and second neoplasms produced by the intensity of therapy or the prolonged delivery of alkylating agents.

In spite of the considerable evolution through innovations in the primary management of various stages, treatment of relapsing Hodgkin's disease is still incompletely defined. The frequent lack of consistent results from salvage therapy is often due to the application of the same or putatively similar treatment to different prognostic subsets. Thus, it is important to clearly define the subsets bearing different prognoses at the time of first treatment failure.

PROGNOSTIC INDICATORS

In untreated Hodgkin's disease certain clinical presentations are widely recognised to bear unfavourable prognostic outcome. The major unfavourable prognostic indicators are tumour mass (e.g. bulky mediastinal and/or para-aortic adenopathy, multiple extranodal involvement, 5 or more splenic nodules), disease progression while on primary chemotherapy and short-term complete remission. In the above mentioned clinical situations the biological implications concern primary drug resistance to one or more classes of cytotoxic agents. Prognosis is also inversely related to age, since children and young adults fare better than older people. In particular, patients aged more than 60 years often present with advanced disease and other medical problems that cause difficulties in the proper staging and treatment of their disease [3]. Recent observations have confirmed that lymphocyte depleted Hodgkin's disease is a rare (5% or less of cases) but very aggressive form of lymphoma whose prognosis is still unfavourable because of widespread nodal and extranodal involvement [4].

The presence of systemic ("B") symptoms carries in general unfavourable prognostic significance, especially in patients with more advanced lymphoma. Patients in stage IIB managed with radiotherapy alone appear to have an adverse outcome when they manifest all three "B" symptoms; this finding is often associated with bulky mediastinal disease [5]. Finally, males almost always have a less favourable prognosis compared with that of females.

In relapsing patients prognosis is mainly related to type of primary treatment and time of treatment failure. In particular, the single most unfavourable prognostic indicator is lack of attainment of complete remission from an intensive multiple drug regimen, particularly when chemotherapy includes non-

Received 21 Jan. 1991; accepted 4 Feb. 1991.

cross resistant regimens such as MOPP (mechlorethamine, vincristine, procarbazine and prednisone) alternated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine).

TREATMENT GUIDELINES

This section will attempt to provide some treatment guidelines related to prognostic subsets for patients requiring salvage treatment.

Patients relapsing from primary radiotherapy probably represent the most favourable category. Usually, combination chemotherapy (single polydrug or alternating regimens) represents the treatment of choice. The complete remission rate and the long-term results are practically superimposable on findings reported for previously untreated patients. In this particular subset the unfavourable prognostic variables are represented by short progression-free intervals, age greater than 50 years and advanced relapse stage (e.g. multiple visceral involvement) [6]. In complete responders it is doubtful whether the addition of radiotherapy can further improve treatment outcome [7].

For optimal treatment decision-making, in Hodgkin's disease relapsing from primary chemotherapy it is advisable to subdivide patients into three prognostic categories [8]: lack of initial complete remission, complete remission lasting for less than 12 months and complete response for longer than 12 months. Depending on whether primary chemotherapy consisted of a single polydrug vs. an alternating or hybrid programme, the fraction of patients not achieving first complete remission varies from a maximum of 30% to a minimum of less than 15% [2, 8]. The prognostic characteristics of patients not achieving complete remission as a result of primary drug resistance appear clinically related to a number of known variables, the most consistent of which is tumour cell burden, expressed by number of anatomically involved sites and/or bulky adenopathy. Regardless of type of chemotherapy used, the vast majority of lymphomas in this category are truly resistant, for salvage chemotherapy yields poor outcome. In fact, the 3-year freedom from progression after conventional second-line treatment is 10–15% and may increase to 30–35% only after high-dose chemotherapy combined with autologous bone marrow transplantation (ABMT) [8].

An intermediate form of clinical resistance is represented by a situation in which primary treatment attains first complete remission whose unmaintained duration lasts for fewer than 12 months. In this subset, salvage chemotherapy should consist of a non-cross resistant regimen. Following primary MOPP, salvage ABVD can yield complete remission in about 65% of patients while 35% of them remain alive and disease-free at 5 years. Comparable results were reported after B-CAVe (bleomycin, lomustine, doxorubicin and vinblastine). The same frequency of response occurs in ABVD-salvage MOPP. Treatment findings are superior in the presence of relapsing lymphoma limited to less than three nodal sites compared with those in patients with extensive nodal and extranodal involvement as well as systemic symptoms. Both magnitude and duration of complete remission can be compromised if a single drug regimen and/or radiation are utilised as first salvage treatment, i.e. before ABVD, B-CAVE or MOPP, respectively. When primary chemotherapy includes both MOPP and ABVD (alternating or hybrid programmes) salvage treatment with conventional drug regimens [e.g. lomustine, etoposide and prednimustine (CEP) or mytoguazone, ifosfamide with mesna and etoposide (MIME)] usually yields poor outcome. In this particular prognostic subset, superior results can now be achieved only through high-dose chemotherapy with ABMT or peripheral blood stem cell support [8–10]. In fact, in our own experience with MOPP/ABVD, salvage high-dose chemotherapy with bone marrow rescue yielded 3-year freedom from second progression of 76% [8].

A third category with less clinical resistance is represented by patients whose disease relapse occurs after an initial complete remission of longer than 12 months. In this subset, retreatment with the same drug regimen utilised as primary chemotherapy can induce a second complete tumour response in more than three quarters of cases and the 5-year freedom from second relapse is about 50% [7]. Theoretically, it is possible that intensive treatment with ABMT will achieve better results. For this reason, it is worth testing high-dose chemotherapy in patients selected for their unfavourable relapse stage.

CONCLUSION

In the salvage treatment of Hodgkin's disease the definition of prognostic categories will contribute to assessment of which clinical situation may require a given type or intensity of treatment. Clinical categories or prognostic subsets should remain clearly distinct when treatment strategies are devised and results of salvage therapies reported. In fact, the discrepancies between a given treatment and its results may reflect, in part, the discrepancies in patient selection among institutions and study groups testing the same or putatively similar treatment regimens. It is also important to stress that in a regression analysis, taking into account the type of response to primary chemotherapy besides other prognostic factors, the degree of response to initial chemotherapy remains an important indicator of treatment outcome when analysed both singly and in the presence of known variables.

Gianni Bonadonna
Division of Medical Oncology
Istituto Nazionale Tumori
20133 Milan, Italy

1. Bonadonna G, Valagussa P. Influence of clinical trials on current treatment strategy for Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1990, **19**, 209–218.
2. Lippman ME, Yee D, eds. The lymphomas: current concepts in pathogenesis and management. *J Natl Cancer Inst Monographs* 1990, **10**, 1–82.
3. Austin-Seymour MM, Hoppe RT, Cox RS, *et al.* Hodgkin's disease in patients over sixty years old. *Ann Intern Med* 1984, **100**, 13–18.
4. Kant JA, Hubbard SM, Longo DL, *et al.* The pathologic and clinical heterogeneity of lymphocyte-depleted Hodgkin's disease. *J Clin Oncol* 1986, **4**, 284–294.
5. Crnkovich MJ, Hoppe RT, Rosenberg SA. Stage IIB Hodgkin's disease: the Stanford experience. *J Clin Oncol* 1986, **4**, 472–479.
6. Roach M. III, Brophy N, Cox R, *et al.* Prognostic factor for patients relapsing after radiotherapy for early-stage Hodgkin's disease. *J Clin Oncol* 1990, **8**, 623–629.
7. Viviani S, Santoro A, Negretti E, *et al.* Salvage chemotherapy in Hodgkin's disease. Results in patients relapsing more than twelve months after first complete remission. *Ann Oncol* 1990, **1**, 123–127.
8. Bonadonna G, Santoro A, Gianni AM, *et al.* Primary and salvage chemotherapy in advanced Hodgkin's disease: The Milan Cancer Institute experience. *Ann Oncol* 1991 **2**(Suppl. 1) 9–15.
9. Jones RJ, Piantadosi S, Mann RB, *et al.* High-dose cytotoxic therapy and bone marrow transplantation for relapsed Hodgkin's disease. *J Clin Oncol* 1990, **8**, 527–537.
10. Hurd DD, Haake RJ, Lasky LC, *et al.* Treatment of refractory and relapsed Hodgkin's disease: intensive chemotherapy and autologous bone marrow or peripheral blood stem cell support. *Med Ped Oncol* 1990, **18**, 447–453.