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Survival in Hodgkin's disease patients – Report of 25 years of experience at the Milan Cancer Institute

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Abstract

The aim of this study was to assess the long-term therapeutic outcome and risk of treatment-related complications in Hodgkin's disease. From May 1973 to September 1990, four randomised studies have been activated at the Milan Cancer Institute using nitrogen mustard, vincristine, procarbazine and prednisone (MOPP) and doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) regimens, with or without irradiation, involving a total of 811 patients with intermediate and advanced Hodgkin's disease. Overall, ABVD contributed to significantly reduce the relative risk of lymphoma progression and death compared with the MOPP regimen. With a prolonged follow-up, a total of 106 patients (75 of whom were in continuous complete remission after first-line chemotherapy) developed a variety of cancers, resulting in a total risk of 22.2%. Our 25 years of experience re-emphasises that ABVD can cure a high fraction of patients with Hodgkin's disease. However, patients in continuous complete remission, are at a high risk of developing second cancers, especially when the treatment strategy includes extensive irradiation. The main focus of future trials should be on reducing treatment sequelae to improve the quality of life of long-term survivors.

Keywords: ABVD; Causes of death; Hodgkin's disease; MOPP; Second cancers

1. Introduction

Before 1960, chemotherapeutic agents to treat Hodgkin's disease were used only for palliation. In 1964, the nitrogen mustard, vincristine, procarbazine, prednisone (MOPP) scheme was conceived, being the first regimen that achieved cure in a proportion of patients with advanced lymphoma [1,2]. It represented a milestone for intermittent combination chemotherapy in the treatment of cancer. The observation that approximately 20% of the treated patients failed to achieve complete remission of their lymphoma, coupled with the relative insensitivity of the tumour in patients who experienced short remissions, suggested that the primary cause of treatment failure was the presence and overgrowth of cells resistant to the drugs in the MOPP regimen.

In the attempt to overcome this resistance, a new four-drug regimen known as doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) was designed and tested at the Milan Cancer Institute [3]. The selection of the four agents was based on evidence of the anti-lymphoma properties of each individual drug and on their non-overlapping sensitivity profiles with MOPP. The strategy utilised in the development of ABVD-containing regimens consisted of different phases (Table 1). In Study 1, we compared the efficacy of ABVD *vs.* MOPP in advanced Hodgkin's disease previously untreated with chemotherapy and, through a cross-over design, we tested either regimen in resistant patients [4]. Study

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Table 1
Summary of randomised studies with MOPP and ABVD regimens carried out at the Milan Cancer Institute

Enrolment period	Hodgkin's disease stage	Prior radiotherapy failures	Study design	No. of chemotherapy cycles	Radiotherapy planned	No. of patients
Study 1						
May 1973 to September 1974[4]	IIB, III, IV	Eligible	MOPP *vs.*	6	Extensive	41
			ABVD	6	Extensive	35
Study 2						
September 1974 to June 1982[5]	IIB, III	Not eligible	MOPP *vs.*	6	Extensive[a]	114
			ABVD	6	Extensive[a]	118
Study 3						
October 1974 to May 1982[6]	IV	Eligible	MOPP *vs.*	12	No	43
			MM/AA	12	No	45
Study 4						
June 1982 to September 1990[7]	IB, IIA bulky, IIB, III, IV	Eligible	MM/AA *vs.*	To CR plus 2	Bulky area(s)	211
			MA/MA	To CR plus 2	Bulky area(s)	204

MOPP, nitrogen mustard, vincristine, procarbazine, prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; MM/AA, one full monthly cycle of MOPP alternated with one full monthly cycle of ABVD; MA/MA, half cycle of MOPP alternated with half cycle of ABVD; CR, complete remission.
[a] Delivered after the first three cycles of either combination.

2 aimed at assessing the relative efficacy and long-term complications of a combined modality approach with three cycles of either MOPP or ABVD delivered before and after extensive irradiation in patients with stage IIB and III disease [5]. In Study 3, we elected to alternate one cycle of MOPP with one cycle of ABVD (MM/AA) as first-line treatment in patients with pathological stage IV disease in the attempt to increase the percentage of durable complete remissions compared with MOPP [6]. In the early 1980's, a new trial (Study 4) was activated aimed at assessing whether a more rapid alternation of the eight drugs (half cycle of MOPP and half cycle of ABVD, MA/MA) could improve treatment outcome compared with MM/AA [7].

We summarise here, our 25-years of experience, reporting both treatment outcome and long-term complications for each regimen.

2. Patients and methods

Study designs of the randomised trials have already been detailed in previous publications [4–7] and are summarised in Table 1. Briefly, the study population consisted of consecutive patients admitted at the Milan Cancer Institute with a biopsy-proven diagnosis of Hodgkin's disease and previously untreated with chemotherapy. Irradiation was part of the treatment programme in all studies but Study 3, which was carried out in patients with stage IV disease. Extensive irradiation (either total or subtotal nodal radiotherapy according to disease presentation) was delivered in Study 1 and 2 [4,5], while in Study 4 [7] irradiation was limited to the nodal areas defined as bulky (mediastinal mass greater than 1/3 the thoracic diameter and/or nodal disease >10 cm).

The study designs were approved by the members of the institute's research and ethics committees and, according to the Italian rules at the time, all patients had to give their verbal informed consent prior to being enrolled into each of the studies.

2.1. Chemotherapy regimens

MOPP therapy was administered every 4 weeks at the classical dose schedule designed at the National Cancer Institute (nitrogen mustard and vincristine delivered intravenously at the dose of 6 and 1.4 mg/m^2, respectively, on days 1 and 8; procarbazine and prednisone delivered orally at the dose of 100 and 40 mg/m^2, respectively, from day 1 to 14 of each treatment cycle) [1]. When originally designed [3], ABVD consisted of the administration of doxorubicin (25 mg/m^2), bleomycin (10 mg/m^2), and vinblastine (6 mg/m^2), all three drugs delivered intravenously on days 1 and 15, every 4 weeks. Dacarbazine was initially given intravenously at the dose of 150 mg/m^2 given on days 1–5 and 15–19. Later [5–7], the administration of dacarbazine was modified to 375 mg/m^2 on days 1 and 15 to facilitate the delivery of ABVD and to improve the quality of life of the treated patients. The alternating administration of MOPP and ABVD (MM/AA) consisted of one full cycle of either regimen every 4 weeks, while the hybrid version consisted of half cycle of MOPP on day 1 (with procarbazine and prednisone continued to day 7) and half cycle of ABVD on day 15, followed by a 2-week rest period.

2.2. Staging procedures

Clinical staging consisted of physical examination, complete blood cell count, liver and renal function tests,