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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,

postero–anterior and lateral chest X-ray, and bipedal lymphangiography. Additional X-rays or radioisotopic studies were performed only in the presence of certain clinical situations. Computerised tomography (CT) and gallium scans were not in use during the accrual period of the reported studies and were performed in only a few patients in the last trial. In addition to biopsy of the peripheral lymph nodes, invasive tests for pathological staging included needle bone marrow core biopsies from bilateral iliac crests in the vast majority of the patients. The abdominal extent of disease was evaluated through staging laparotomy in newly diagnosed patients up to the autumn of 1976, when it was replaced by staging laparoscopy to detect or rule out liver and splenic involvement. All patients failing on prior irradiation underwent staging laparoscopy.

2.3. Follow-up evaluation and response assessment

All patients had a physical examination and a complete blood count before each drug administration. In the absence of suspicious findings, physical examination, routine laboratory tests, chest X-ray and plain film of the abdomen, as well as lymphangiogram (until residual lymphangiographic contrast was present), were repeated every 3 months during the first 2 years after completion of therapy, every 6 months during years 3–5, and once a year thereafter. After the 15th year of follow-up, examinations were planned every 12–24 months, and when they were not directly performed in the outpatient clinic of the Institute, contacts were periodically maintained with the patients themselves and with their family doctors. In patients with suspicious or controversial findings, examinations were performed more often.

Treatment response was assessed clinically and by repeating all studies that were positive at diagnosis.

2.4. Second-line treatments

In Study 1, activated in 1973, planned second-line treatment consisted of crossing to the alternative regimen [4]. In all other studies, patients who relapsed after a complete remission that lasted more then 12 months were planned to receive re-treatment with the same regimen, with or without additional irradiation according to the site(s) of disease relapse and feasibility. Patients who showed disease progression while on treatment or disease relapse within 12 months were considered resistant to the primary chemotherapy regimen and were planned to receive the alternative regimen if treated with MOPP or ABVD or to a combination including lomustine (CCNU), etoposide and prednimustine (CEP) [8], with or without additional irradiation. According to the individual clinical situations, starting from 1985, selected patients (age < 55 years, no detectable bone marrow involvement, Karnofsky performance status >70, no or limited irradiation) were given high-dose chemotherapy plus autologous bone marrow reinfusion [9].

2.5. Statistical analysis

Freedom from progression was calculated from the date of starting chemotherapy to the first documented evidence of treatment failure. Death from all causes was used as the end-point for overall survival, which was also measured from the date of starting chemotherapy. The Kaplan–Meier [10] product-limit method was adopted. The null hypothesis concerning the differential effects of treatment was tested in univariate analysis by means of the log-rank test [11] and all P values were two-tailed. The rates of the second malignancies and cause-specific death were measured from the date of starting chemotherapy to the date of the event considered and were calculated according to the method proposed by Marubini and Valsecchi [12]. All estimates of freedom from progression, survival and cumulative risks are reported with the 95% Confidence Intervals (CI).

All data relative to the studies herein reported have been managed and analysed according to the standard operating procedures of the Operations Office of the Istituto Nazionale Tumori in Milan.

The present analysis was carried out on data available as of February 28, 2004. A total of 365 patients were alive in continuous complete remission and had not developed a second cancer. Follow-up information were complete in all of these patients, but for 29 of them (8%) the time elapsed between the date of last contact and the date of present analysis exceeded 2 years.

3. Results

The long-term results for freedom from progression and risk of dying for Hodgkin's disease are reported in Table 2 for each of the four consecutive studies. In Study 1, after a median follow-up of 29 years, freedom from progression accounted for 46% after MOPP and for 58% after ABVD, representing a relative reduction of approximately 30% favouring the ABVD arm. For both treatment regimens, the vast majority of failures were observed during the first 5 years from starting chemotherapy. A total of 13 patients developed second malignancy, nine while in first complete remission (MOPP: 5, ABVD: 4). Details and risk of second cancers will be described later. After approximately three decades of follow-up, the risk of dying for progressive lymphoma was 49% after MOPP and 29% after ABVD. It is important to note that no deaths caused by progressive lymphoma were documented after 12 years from starting either MOPP or ABVD.

Study 2 was activated in September 1974 and three cycles of either MOPP or ABVD were delivered before

Table 2
Long-term results

Study	Median follow-up (years)	Freedom from progression		Risk of dying for Hodgkin's disease		No. second cancers	
		%	(95% CI)	%	(95% CI)	Leukaemia	Solid tumours
Study 1	29						
MOPP-ERT		46	(30–63)	49	(28–61)	3 (2)	4 (3)
ABVD-ERT		58	(39–76)	29	(13–45)	0	5 (4)
Study 2	25						
MOPP-ERT-MOPP		56*	(49–68)	35*	(26–45)	4 (2)	8 (5)
ABVD-ERT-ABVD		78*	(70–86)	15*	(9–22)	2 (2)	17 (17)
Study 3	25						
MOPP		31**	(16–45)	46***	(30–61)	1 (1)	3 (1)
MM/AA		58**	(42–73)	27***	(13–40)	1 (0)	7 (6)
Study 4	16.7						
MM/AA-RTB		65	(59–71)	22	(12–32)	7 (1)	16 (13)
MA/MA-RTB		70	(64–76)	19	(13–25)	9 (2)	19 (16)

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; ERT, extensive irradiation; RTB, radiotherapy to the area(s) of bulky disease; 95% CI, 95% Confidence Interval.
( ) Number of patients who developed second cancer while in continuous complete remission from first-line chemotherapy.
* $P = 0.002$.
** $P = 0.003$.
*** $P = 0.07$.

and after extensive irradiation. As reported in Table 2, at a median follow-up of approximately 25 years from starting chemotherapy, a significantly higher fraction of patients remained free of Hodgkin's disease after ABVD (78%) compared with MOPP (56%, $P = 0.002$), with a relative reduction in the risk of disease relapse of approximately 65%. In both treatment arms, the risk of new lymphoma manifestations was higher during the first 4 years from starting chemotherapy and declined thereafter. The risk of dying from Hodgkin's disease was more than double after MOPP (35%) compared with ABVD (15%, $P = 0.002$), and, as observed in the previous case series, deaths due to progressive lymphoma were almost exclusively documented during the first 6.5 years from starting protocol treatment. A total of 30 second cancers were documented, 12 in the MOPP group and 17 in the ABVD group.

Study 3 compared MOPP alone with alternated MM/AA in stage IV patients. At a median follow-up of 25 years, more than half patients remained free from Hodgkin's disease after MM/AA (58%), compared with MOPP alone (31%), representing a relative reduction in the risk of disease relapse of 58% (95% CI, 24–77, $P = 0.003$). A total of 13 patients (MOPP: 4, MM/AA: 8) presented with second malignancies, eight developing while the patients were in their first complete remission (see below for details). The risk of dying for Hodgkin's disease was 46% after MOPP and 27% after MM/AA ($P = 0.07$).

In Study 4, a minimum of six cycles of MOPP and ABVD were delivered in two different sequences. In one arm, half cycle of MOPP and half cycle of ABVD (MA/MA) were administered every month and were compared with the monthly alternating administration of one full cycle of the two combinations (MM/AA). A total of 415 evaluable, chemotherapy-naïve, consecutive patients with pathological stage IB, IIA bulky, IIB, III and IV were randomly allocated to either of the two regimens. After a median follow-up of 16.7 years, no statistically significant differences were detected in either freedom from progression (MM/AA: 65%, MA/MA: 70%) or in the risk of dying for progressive lymphoma (MM/AA: 22%, MA/MA: 19%). In both treatment arms, the risk of developing new lymphoma manifestations was highest during the first 3 years from starting treatment, and the risk of dying for progressive disease was mainly observed during the first 10 years.

3.1. Risk of second malignancies

The long-term follow-up of our case series allows us to attempt assessing the relative risk of second malignancies according to the chemotherapy regimen delivered as first-line treatment. Overall, within 25 years, 106 patients developed a second tumour, 75 second cancers being documented in patients in continuous complete remission from first-line chemotherapy. As displayed in Fig. 1, the total cumulative risk was 22.2% (95% CI, 17.8–26.7). Twenty-seven patients developed secondary leukaemia (24 patients) or myelodysplastic syndrome (three patients), the total risk accounting for 4.5% (95% CI, 2.8–6.2). The risk of developing second solid tumours was 17.7% (95% CI, 13.3–22.1). As can be seen from Fig. 1, almost all cases

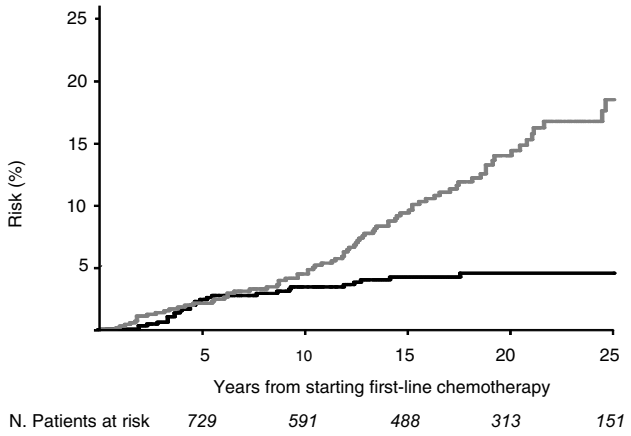

Fig. 1. Risk of secondary leukaemia (black) and solid tumours (grey) in the entire case series of 811 patients. In italics, number of patients at risk at 5-year intervals.

of leukaemia or myelodysplastic syndrome developed within the first decade from starting first-line chemotherapy, while the risk for all solid cancers started to increase after the 9th year. The total cumulative risk for leukaemia and for solid tumours according to the first-line chemotherapy regimen delivered is displayed in Fig. 2. Table 3 reports the number of second tumours documented, and whether or not patients received irradiation or salvage chemotherapy during the entire course of their disease. Eight patients developed secondary leukaemia after primary MOPP for a cumulative risk of 6.2% (95% CI, 2.1–10.3); all had received irradiation and three additional salvage chemotherapy for lymphoma progression. In the ABVD group, one patient developed a secondary leukaemia and a second one a myelodysplastic syndrome, for a total risk of 1.7% (95% CI, 0–3.1). Both patients received irradiation and both were in first complete clinical remission of their Hodgkin's disease. In patients given alternating or hybrid MOPP and ABVD, two myelodysplastic syndromes and 15 secondary leukaemias were documented for an overall risk of 5.0% (95% CI, 2.5–7.5). Fourteen patients received irradiation during the course of their disease, and 13 were given salvage chemotherapy for lymphoma progression or relapse. Of note, seven patients received CEP chemotherapy with or without additional radiotherapy and two patients received salvage high-dose chemotherapy.

The total cumulative incidence of solid tumours was 13.2% (95% CI, 6.1–20.2) after primary MOPP, 22.1%

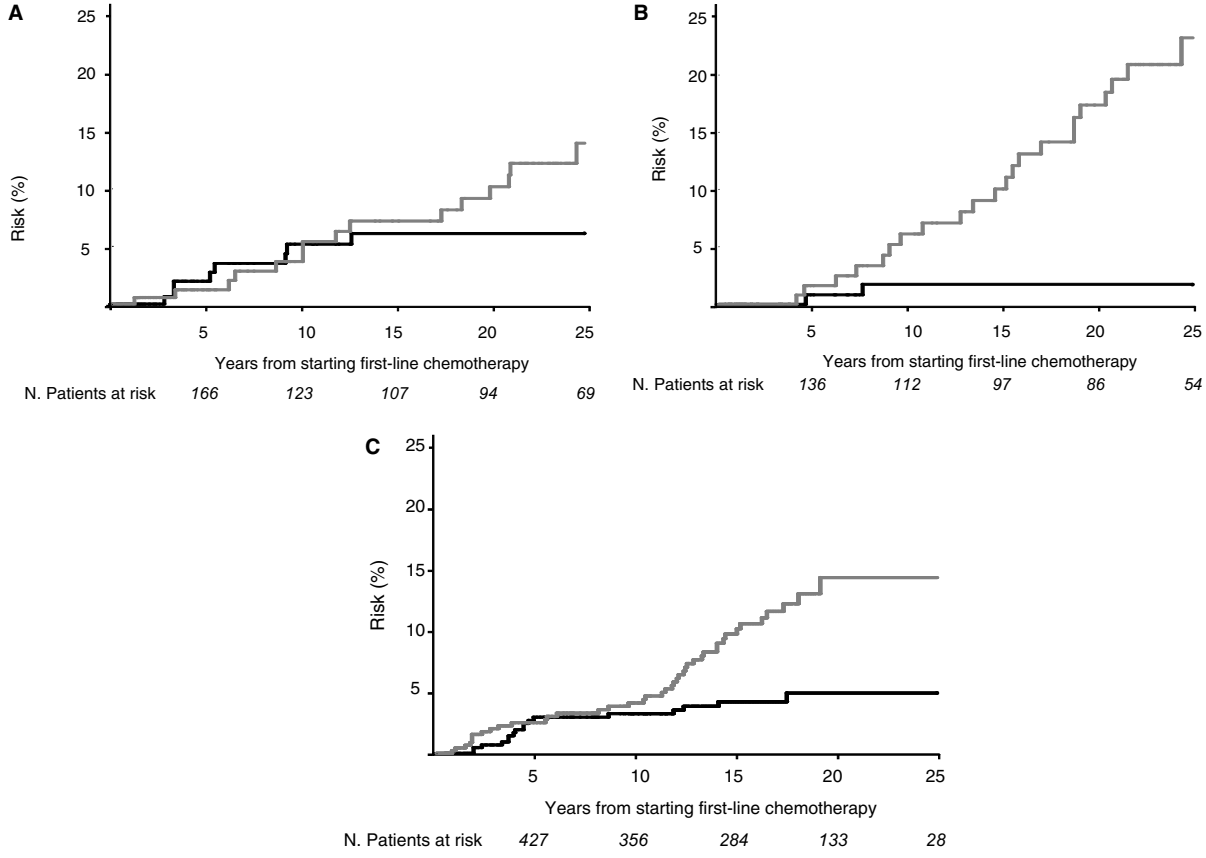

Fig. 2. Risk of secondary leukaemia (black) and solid tumours (grey) according to chemotherapy regimen: A: nitrogen mustard, vincristine, procarbazine and prednisone (MOPP); B: doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD); C: MOPP/ABVD. In italics, number of patients at risk at 5-year intervals.

Table 3
Second cancers documented within 25 years of follow-up

Second cancers	MOPP (198 patients)	ABVD (153 patients)	MOPP/ABVD (460 patients)	Total series (811 patients)
Total cumulative risk (%) (95% CI)	19.4 (12.0–26.9)	24.6 (15.6–33.8)	19.3 (13.9–24.7)	22.2 (17.8–26.7)
Total number	23	24	59	106
Given irradiation[a]	21/153	24/153	37/257	82/563
Salvage chemotherapy	7/92	2/36	15/144	24/272
Leukaemia or MDS	8	2	17	27
Solid tumours				
Non-Hodgkin's lymphoma	3	1	6	10
Lung	2	6	11	19
Breast	2	4	5	11
Gastrointestinal	3	3	8	14
Others	5	8	12	25

95% CI, 95% Confidence Interval.
[a] During the entire course of disease; MDS: myelodysplastic syndrome.

(95% CI, 13.8–32.1) after primary ABVD and 14.3% (95% CI, 9.2–19.3) after alternating or hybrid MOPP and ABVD. A wide variety of second tumours were documented, including lung cancer in a total of 19 patients (11 of whom had received prior mantle irradiation), 14 gastrointestinal cancers (nine in previously irradiated areas), 10 non-Hodgkin's lymphomas (five in previously irradiated areas), and three sarcomas (two in irradiated areas). Eleven female patients developed breast carcinoma (all but one in patients who received previous irradiation) and their median age at the time of starting primary chemotherapy was 28 years (range 20–64 years). Five of these women received chemotherapy because of primary irradiation failure and their median age at starting radiotherapy was 17 years (range 13–28 years).

3.2. Causes of death

Twenty-five years after starting primary chemotherapy, a total of 354 patients of the entire case series were known to have died, representing an overall risk of dying due to all causes of 51.8% (95% CI, 47.1–56.1). One hundred and eighty-two patients died due to progressive lymphoma, for an overall risk of 25.1% (Table 4). The relative risks of dying from progressive lymphoma according to each individual study have been reported in Table 2. Table 4 also reports the number of events for each cause of death and for the primary chemotherapy regimen, as well as the total number of events and the risk of dying for each cause for the total case series of 811 patients. Briefly, a total of 20 patients died for causes directly related to toxicity or complication of either primary or salvage chemotherapy; 67 patients died due to progressive second cancers. Of the remaining patients, 59 died for causes unrelated to Hodgkin's disease or its treatment, while in 26 patients the role of long-term complications due to the delivered treatment could not be ruled out completely. It is worth mentioning that all patients but one in the MOPP group had received irradiation. Among the 19 patients who died for heart-related sequelae, 14 died because of myocardial infarction. Of note, median survival time for pa-

Table 4
Main causes of death within 25 years

Causes of death	MOPP (198 patients)	ABVD (153 patients)	MOPP/ABVD (460 patients)	Total series (811 patients)			
	# events	# events	# events	# events	% risk of dying for the event	(95% CI)	Median time from starting first-line chemotherapy years (range)
Progressive lymphoma	72	26	84	182	25.1	(21.7–28.6)	3.1 (0.2–24.4)
Toxicity from either first-line or salvage chemotherapy	5	10	5	20	2.6	(1.5–3.8)	1.3 (0.3–4.8)
Second cancers	15	15	37	67	11.6	(7.9–15.0)	9.7 (1.2–23.4)
Potentially treatment-related	6	15	5	26	3.4	(0.8–6.0)	12.3 (3.3–24.2)
Lung-related	1	4	0	5			
Heart-related	5	10	4	19			
Others	0	1	1	2			
Unrelated to Hodgkin's disease and its treatment	17	16	26	59	9.1	(5.1–13.1)	12.0 (0.5–24.8)

95% CI: 95% Confidence Interval.

tients who died of potential complications (12.3 years, range 3.3–24.2) was not different from that of patients who died for unrelated causes (12.0 years, range 0.5–24.8).

4. Discussion

With the introduction of effective chemotherapy regimens, such as MOPP in 1964 [1,2] and ABVD in 1973 [3,13], significant advances have been made in the treatment of patients with intermediate and advanced stages of Hodgkin's disease, transforming this malignancy from a previously uniformly fatal disease to a highly curable one. We have summarised here our 25-year experience using MOPP, ABVD or their alternating delivery in a series of successive randomised studies carried out at the Milan Cancer Institute. Of importance, the relative reduction of approximately 50% in the risk of disease progression or relapse favouring ABVD was translated into a similar reduction in the risk of dying for Hodgkin's disease even after such a long follow-up. Our treatment findings, along with those reported in randomised studies conducted by the Cancer and Leukaemia Group B (CALGB) [14] and by the Intergroup Trial [15], confirm that at present ABVD should be considered the standard regimen for the treatment of Hodgkin's disease.

As patients began to survive longer after successful treatments, other problems were documented at a greater frequency that one would expect in an age-matched population. The long-term follow-up of our studies allowed us to attempt assessing two of these important aspects, namely the risk of second cancers and the main causes and risk of death.

In the entire case series of 811 patients, the total risk of developing a second tumour within 25 years from starting first-line chemotherapy accounted for 22.2% and overall we failed to document striking differences relative to the first chemotherapy regimen delivered. However, as shown in Fig. 2, the risk of developing secondary leukaemia or myelodysplastic syndrome was lower after ABVD (1.7%) than after either MOPP (6.2%) or MOPP alternated with ABVD (5.0%). The risk became apparent within the first years and remained elevated for at least 10 years, when it became to decline. These observations are in line with those reported by other authors on the leukaemogenic risk of alkylating-containing chemotherapies [16–18]. As far as other malignancies are concerned, a variety of them were documented and their total risk, accounting for 17.7% at 25 years, rose steadily after the first 10 years and no decline has been observed so far (Fig. 1). Similarly to other case series [16,17,19], the most frequently documented solid tumours were lung, gastrointestinal and female breast cancer. Of concern, the 25-year risk of solid tumours was higher after ABVD (22.1%) than after either MOPP (13.2%) or MOPP alternated with ABVD (14.3%). It is worth emphasising that all the patients given ABVD also received subtotal or total nodal irradiation with doses up to 35–36 Gy and, although the vast majority of solid tumours developed in previously irradiated areas, it is impossible to disentangle the relative contribution of either treatment modality in the observed carcinogenic risk.

A careful review of all medical records, history and death reports allowed us to assess all the causes of death. We purposely avoided any epidemiological study on the excess of risk compared with that of the age-matched general population, but rather attempted to quantify the cumulative risks in the present case series of patients treated under protocol plans with all the stringent requirements for timing and methods of follow-up. The main cause of death remained progressive lymphoma and, regardless of the treatment delivered and prognostic features of various patient subsets, the total risk at 25 years accounted for 25.1%. The risk of dying for progressive disease was almost negligible after the first 10 years, but it was highest during the first 4–5 years from starting first-line chemotherapy, underscoring that tumour cells in this patient subgroup were rather insensitive to both first-line and salvage chemotherapy. A limited fraction of patients (2.6%) died early for toxicity or acute complications of the delivered treatment. In five patients, irradiation fibrosis was the cause of death, while toxicity from both irradiation and bleomycin treatment was documented in two additional patients. Three patients in the ABVD group died from congestive heart failure, pericarditis and myocardial infarction, respectively. In the MOPP/ABVD group, five patients died from toxicity due to salvage chemotherapy and the causes of death in the remaining patients were infections (2), hepatitis (1), pancreatitis (1) and haematological complications (1), respectively.

The risk of dying for progressive second cancers ranked second in our case series: a total of 67 events were documented within the first 25 years, for a total risk of 11.6%, and, as reported in other case series [20,21], started to increase after 10 years of follow-up. Of note, only one of the patients who developed secondary leukaemia achieved complete remission and is presently alive 12 years after the diagnosis of second cancer. Of the 10 patients who developed non-Hodgkin's lymphoma, six died of progressive second malignancy as did 13 of the 19 patients who presented with lung tumours. By contrast, seven of the 11 female patients are presently alive after successful treatment for breast cancer. In a total of 26 patients, the role of late complications from the treatment delivered for their Hodgkin's disease could not be entirely ruled out as cause of death,

for a total risk of 3.4%. They were mainly (19 of 26 or 73%) due to cardiovascular diseases, especially myocardial infarction, and were more frequent in the ABVD group. In the remaining 59 patients, the cause of death was unrelated to either Hodgkin's disease or its treatment. Of note, the median survival time for this group of patients was 12 years (range 0.5 to 24.8 years) and was similar to that observed for patients who died due to late complications (Table 4).

Some aspects of our findings on long-term complications should be interpreted by keeping in mind that they are primarily of historical interest, because they are derived from studies started three decades ago. Overall, the vast majority of our patients received extensive irradiation, including mantle fields and para-aortic and iliac nodes. These wider fields, which were delivered to a much larger proportion of patients than would be considered optimal practice today, may have negatively influenced the risk of second malignancy and the risk of complications due to pulmonary or heart disease. It is reasonable to hope that present reductions in the physical extent of the radiation, coupled with improved dosimetry and radiation delivery, will further reduce excess risks of second cancers and of deaths for complications [22].

However, it is important to maintain some perspective on the appropriate treatment for patients with intermediate and advanced Hodgkin's disease. Approximately one fourth of these patients are at risk of dying from progressive lymphoma: overall, ABVD has been able to substantially reduce this risk by achieving a high fraction of durable complete remissions. One other important finding is that ABVD has a minimal risk of inducing secondary leukaemia, that still today represents a dreadful complication of many alkylating-containing regimens [18].

More intensified regimens, such as escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) [23] or Stanford V [24], may potentially achieve additional therapeutic gains. Whether these gains will be counterbalanced by the negative effects of treatment complications can only be answered through longer follow-up of completed and ongoing trials. We need in fact to carefully adjust the treatment strategy for each patient to properly balance treatment effectiveness with minimisation of the late hazards of that same treatment [22].

Conflict of interest

The authors declare that they have no financial or personal relationships with commercial companies or other organisations.

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