Ten-Year Survival and Late Sequelae in Testicular Cancer Patients Treated With Cisplatin, Vinblastine, and Bleomycin

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This 10-year follow-up study of 91 patients with disseminated testicular nonseminomatous cancer, treated with cisplatin, vinblastine, and bleomycin (PVB) induction chemotherapy and vinblastine plus bleomycin maintenance chemotherapy for a planned period of 2 years, shows a 63% cure rate. The predominant long-term sequelae are neurological and sexual dysfunction in 68% and 40% of patients, respectively. Two patients died of myocardial infarction. Sixteen percent of patients developed hyperten-

sion, 23% Raynaud's phenomenon, and 25% ototoxicity. Despite the long-term side effects, 90% of the patients who responded to a questionnaire are fully employed. This study shows that the maintenance chemotherapy has contributed to the incidence and/or degree of neurotoxicity, hypertension, and renal function disturbance.

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IN 1979 and in 1984 we reported the experience of the Dutch Testicular Cancer Study Group with combination chemotherapy consisting of cisplatin, vinblastine, and bleomycin (PVB) in patients with advanced nonseminomatous testicular cancer.^{1,2} In short, 91 patients were treated with four cycles of PVB induction chemotherapy according to the original Einhorn scheme,³ including high-dose vinblastine, 0.4 mg/kg per treatment cycle. Complete responders were assigned to maintenance chemotherapy with vinblastine, 0.3 mg/kg, alternating with vinblastine, 0.2 mg/kg, plus cisplatin, 50 mg/m² at 3-week intervals for a planned duration of 2 years. The projected 5-year survival² was 72% overall, 95% for complete responders, and 32% for partial responders.

This report provides an update of the survival after a follow-up of 7 to 10 years and presents information on the organ function and psychosocial status of those patients who are still alive.

PATIENTS AND METHODS

After the completion of induction chemotherapy, patients were followed once every 4 weeks in the first year, every 6 weeks in the second year, every 3 months in the third year, every 6 months in the fourth and fifth year, and annually thereafter. Since the minimum follow-up was 7 years (median 8; range, 7 to 10), all patients visited the clinic once a year. The cut-off date for this analysis is October 31, 1986.

Data regarding blood pressure, renal function, fertility, and physical complaints were drawn from the files of the 57 patients who are still alive and free of tumor. In addition, a self-report questionnaire was designed to obtain information on the present quality of life. Participants were asked about past and present employment, education and training, physical condition including specific questions about possible side effects of PVB chemotherapy, sexual function, and psychosocial status. Symptoms possibly related to adverse effects of

treatment were scored on a four-point scale; 0, no symptoms; 1, mild; 2, moderate; 3, severe symptoms. The remaining items were scored on a ten-point scale: 1 denoting the worst and 10 the best possible score.

SURVIVAL

The survival data, calculated by the Kaplan-Meier method, are shown in Fig 1. The minimum follow-up of all patients was 7 years, at which time the absolute survival rates were 63% for the entire patient group, 87% for complete responders, and 11% for partial responders. The projected 10-year survival results are identical. The survival curve for the partial responders is flattened, since only two patients in the tail of the curve have achieved a complete response with salvage chemotherapy and are still alive and free of tumor.

Causes of Death

Of the 91 patients, 34 have died. Five died of toxicity during induction chemotherapy, four of early progressive disease, and 17 partial responders could not be salvaged. Five patients relapsed and died after 7 to 67 months. Of note, the patient who died at 67 months had an

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Fig 1. Survival curves calculated by the Kaplan-Meier method.

unresectable mature teratoma (teratoma differentiated) and died of a vena cava superior syndrome. Two patients in complete response died of myocardial infarction after 16 and 62 months. One patient developed a second malignancy in the form of an acute nonlymphocytic leukemia, which appeared to be refractory to chemotherapy. He died at 79 months.

Renal Function

Serum creatinine levels were used as the parameter for the assessment of renal function at each check-up. For each patient the average serum creatinine level was calculated for each year of follow-up. Patients with an increase of more than 20% above the first year's average and those with annual values above 120 $\mu\text{mol/L}$ (1.4 mg/dL), which is the upper limit of normal in the participating hospitals, were considered as hav-

ing developed renal function insufficiency. Twelve patients (21%) showed relative increments of 24% to 93% (Table 1). In eight of the 12 patients no further deterioration of renal function occurred after the second year, that is after the completion of maintenance chemotherapy. Only four patients remained with serum creatinine levels above 120 $\mu\text{mol/L}$.

Cardiovascular Symptoms

Two patients, aged 45 and 47 years, died of myocardial infarction while in complete response. They did not have a history of angina pectoris or other cardiovascular problems. Autopsy was performed in one patient. There was no coronary artery sclerosis. A third patient, who was 45 years old at the time of induction chemotherapy, experienced angina pectoris during episodes of anemia. His symptoms have not recurred during a follow-up period of more than 8 years. Another patient, presently 58 years of age, who abuses nicotine and alcohol, suffers from claudication intermittens.

Hypertension was defined as a diastolic blood pressure of 95 mm Hg and above, measured at three different time points according to World Health Organization (WHO) criteria.⁴ This was observed in ten of 56 patients (18%), one of whom was known with pre-existent essential hypertension. The highest recorded blood pressure in this group was 195/115 mm Hg; the average was 180/105. Three of these patients (Table 1, patients no. 31, 32, and 34) also had renal insufficiency. The average increase of diastolic blood pressure in the hypertensive patients

Table 1. Mean Serum Creatinine Levels ($\mu\text{mol/L}$) at Yearly Intervals

Patient No.	Interval (yr)									
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10
3	80	99	105 (31)	109	104	95	96	—	99	
20	73	100	95 (30)	97	101	111	104			
24	66	84 (27)	103 (56)	87	94	97	105			
27	62	79	78 (26)	81	88	91	93	98 (58)		
30	90	99	139 (54)	128	120	127	129	—		
31 ^H	79	93	101 (28)	99	79	103	98			
32 ^H	62	78	82 (32)	83	81	79	83			
34 ^H	87	113	112 (29)	150	150	157	—	153 (76)		
35	87	94	110 (26)	108	105	104	109			
46	90	93	90	98	122	103	111	92	123	124 (36)
53	55	98	99 (80)	95	102	107	101	106		
57	69	94	90 (30)	95	91	101	94	128	119 (72)	

NOTE. Figures in parentheses indicate percent increase above first year's average.

Abbreviation: H, hypertension.

was 22.5 mm Hg as compared with 8.7 mm Hg in the nonhypertensive patients.

Raynaud's Phenomenon

Raynaud's phenomenon was reported in 13 patients (23%), based on history and physical signs. Angiograms were not performed.

Fertility

Semen analyses were performed inconsistently. Nine couples conceived 15 healthy children after the completion of chemotherapy. A 16th child was delivered after artificial insemination with previously banked semen. In one case a spontaneous abortion occurred in the sixth week of pregnancy.

QUESTIONNAIRE

A questionnaire was sent to all 57 long-term survivors, 48 of whom (84%) completed and returned the document.

Physical Condition

Twenty-six patients (54%) reported a decrease of physical condition described as easy fatigability during work or exercise, paresthesia, and decreased muscle strength. The mean score for physical condition before the disease was 8.4 (median, 8.5); the present mean score is 7.6 (median, 7.5). Three patients reported an improvement of physical condition.

Symptoms of peripheral polyneuropathy, either chronic or intermittent, were reported by 68%. Half of the participants reported some degree of impaired motor function.

Ototoxicity was reported by 12 participants (25%), half of them with tinnitus only, four with a hearing loss in the speech frequency, and two patients with a low- and high-pitch hearing loss as well as tinnitus.

Sexual Life

Nineteen patients (40%) experience a deterioration of their sexual life; 6 (13%) reported an improvement. Seven patients (15%) are dissatisfied with their sexual life after treatment. The mean score for sexual life before the disease was 8.1 (median, 8); the present mean score is 7.1 (median, 7).

Ten patients (21%) developed decreased sexual desire (Table 2). Four patients (8%) developed problems with erection, and another 15 (31%) have experienced ejaculation distur-

bances. Some of these patients spontaneously reported less satisfaction of their orgasm.

Social Status

All 48 respondents were occupied before their disease; three were students, three had a part-time job and were in training for a higher function, and 42 were fully employed.

The mean time to resume work was 14 months (median, 12; range, 2 to 72). Almost all patients indicated that the duration of the work interruption was due to physical complaints from maintenance chemotherapy. A group of 11 patients wanted or had to change their job, which partly influenced the duration of overall time of interruption of work. At the time of the questionnaire, five respondents were still unemployed. Three of them receive disability pension; one because of polyneuropathy following induction and salvage chemotherapy, one because of aspecific low back pain, and the third who is the nicotine and alcohol abuser with claudicatio intermittens.

DISCUSSION

Fifty-seven of 91 patients are alive and disease-free after a follow-up of 7 to 10 years, which indicates a cure rate of 63%. Of the 63 complete responders, five (8%) relapsed and died. All but one relapse occurred within 2 years of induction chemotherapy. The patient who relapsed after 2 years had unresectable mature teratoma (teratoma differentiated) in the mediastinum. These survival and relapse data are in accordance with other reports.⁵⁻¹²

One patient developed acute nonlymphocytic leukemia about 5 years after cessation of chemotherapy. The disease was refractory to chemotherapy. It is likely that this leukemia was secondary to the previous chemotherapy.¹³⁻¹⁶ The karyotype showed nonrandom chromosomal aberrations involving chromosomes 3, 5, and 7.¹⁷

Using serum creatinine levels as a parameter

Table 2. Past and Present Status of Sexual Life

	No. of respondents					
	Before Treatment			Present		
	Yes	Some-times	No	Yes	Some-times	No
Sexual desire	45	2	1	35	13	—
Ability of erection	46	—	2	42	5	1
Ability of orgasm	46	1	1	46	1	1
Ability of ejaculation	46	1	1	31	3	14

for renal function injury, we have previously reported a 20% incidence of renal function impairment (creatinine above 120 $\mu\text{mol/L}$; 1.4 mg/dL) during the phase of induction chemotherapy.² The present analysis shows that only four (7%) of the long-term survivors remain with serum creatinine concentrations above 120 $\mu\text{mol/L}$ (1.4 mg/dL). Nevertheless, 12 patients (21%) have developed relative increments of 24% to 93% in creatinine levels above their first year's average. Given that creatinine is a relative insensitive parameter,^{18,19} this finding suggests that the maintenance therapy with cisplatin has substantially contributed to the damage from induction chemotherapy.

Ischemic cardiovascular events have been reported on rare occasions following chemotherapy with vinblastine alone,^{20,21} vinblastine and bleomycin,^{22,23} and with PVB.^{24,25} In this series, two complete responders died of myocardial infarction. The first one was still on maintenance chemotherapy at that time. The second one was off treatment for over 4 years. These deaths may have been related to the chemotherapy, even though evidence of coronary artery sclerosis, hypertension, symptoms of angina, and hypomagnesemia were absent.^{25,26}

Hypertension (diastolic blood pressure above 95 mm Hg) developed in nine of 56 patients (16%), three of whom showed renal function impairment. The average annual increase in diastolic blood pressure in both hypertensive and nonhypertensive patients (2.8 and 1.09, respectively) is higher than reported in a Danish study.¹⁹ In that report, the nonhypertensive patients had increases similar to those of matched controls: 0.80 mm Hg per year. Although the incidence of hypertension is strikingly similar in the two studies, the degree of hypertension is more severe in our patient group, which may be explained by the maintenance chemotherapy in our patients who received a median of 200 mg/m² of cisplatin more than the Danish patients.

Raynaud's phenomenon was seen in 13 patients (23%). The role of hypomagnesemia, decreased renal plasma flow, increased plasma renin and aldosterone could not be assessed in this study.^{12,26-28} The median duration of maintenance therapy in these patients was 2 months longer than in patients who did not develop these symptoms.

It has been shown that approximately half of the patients (range, 25% to 95%) have a significant reduction of spermatogenesis at the time of tumor diagnosis, rendering about two thirds of all patients as unsuitable candidates for sperm banking.²⁹⁻³⁸ Following induction chemotherapy some degree of recovery will occur in half of the treated patients, mostly after 1 to 3 years.^{9,31,35,36} Available data suggest that about 30% of patients may regain the capacity to father children.^{30,36,39} In this series, nine patients fathered 15 children who were healthy. No increased risk of congenital malformation seems to exist.^{36,39}

Over half of the 48 patients who filled out the questionnaire indicated easy fatigability, paresthesia, and decreased muscle strength. This should also be viewed in the light of the maintenance chemotherapy with cisplatin and vinblastine, which was given for a median of 12 months. To date, the major reason for taking patients off maintenance therapy was neurotoxicity.

Chronic ototoxicity has been reported by 12 patients (25%); six have persistent dullness of hearing. These data are in accordance with investigations based on audiograms.^{40,41} Ototoxicity is not reversible.⁴¹

Despite the problems described, 43 of 48 patients (90%) are fully employed, although some had to change to jobs with less physical strain.

The quality of sexual life decreased in 40% of the respondents, whereas 12% reported to be dissatisfied. Retroperitoneal surgical procedures account for most of the problems with erection and ejaculation.^{42,43} Anejaculation has been found to induce psychosocial distress.^{44,45}

This study shows that maintenance chemotherapy with cisplatin and vinblastine has contributed to the neurotoxicity, as we have demonstrated in another study.⁴⁶ Probably the same holds true for hypertension and renal function disturbance.

It is likely that the omission of maintenance chemotherapy and the substitution of etoposide for vinblastine will benefit the long-term overall condition of patients who are cured today.^{10,38,42,47-49}

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