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Combination chemotherapy in malignant non-seminomatous germ-cell tumors: results of a cooperative study of the German Society of Pediatric Oncology (MAKEI 83)*

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Summary. In January 1983, the German Society of Pediatric Oncology started a cooperative trial (MAKEI 83) for non-testicular germ-cell tumors. The pilot phase closed in December 1985. The treatment regimen was stratified according to histology, tumor site and tumor stage. In malignant non-seminomatous germ-cell tumors (mNSGCTs), chemotherapy consisted of four courses of 3 mg/m^2 vinblastine, on days 1 and 2 and 15 mg/m^2 bleomycin on days 1–3, given by continuous infusion, and 20 mg/m^2 cisplatin on days 4–8 with mannitol diuresis. Courses were repeated every 3 weeks. In mNSGCT patients with ovarian FIGO stages III-IV or extragonadal primaries, second-look surgery was carried out, followed by four additional courses of chemotherapy with 100 mg/m^2 VP-16 on days 1–3, 1.5 g/m^2 ifosfamide on days 1–5 with mesna uroprotection and 20 mg/m^2 cisplatin on days 1–5 with mannitol diuresis. In patients with sacrococcygeal germ-cell tumors, en bloc resection of the tumor, including the coccygeal bone, was mandatory. During the registration period, 57 patients with mNSGCTs were entered: 37 protocol patients and 20 follow-up patients. The event-free survival for protocol patients at 57 months was 78%±6% and that for follow-up patients was 40%±10% (Kaplan-Meier); the crude survival for both groups was 83%±6% and 54%±12%, respectively. After a review by a panel of pathologists, the histological diagnoses in 7% of all registered cases of germ-cell tumors were changed. The results of the present studies show that the histological subclassification of mNSGCTs, tumor site and tumor stage no longer had prognostic value.

Introduction

In the past, mNSGCTs had a very poor prognosis and had caused about 3% of deaths from malignancy in infancy and childhood [43]. In spite of combined treatment consisting of surgery, irradiation and chemotherapy with different agents, >90% of patients died within 2 years [20, 32, 41]. Therapy regimens including vincristine, actinomycin D and cyclophosphamide (VAC) plus/minus Adriamycin at high doses [15, 28, 41] led to a long-term remission in about half of the patients.

Combined therapy according to Einhorn and Donohue [13], including vinblastine, bleomycin and cisplatin (VBC) has proved to be very effective in adults with testicular cancer. This strategy has also been successfully used in infants and children [28, 31, 33] but was associated with an increased risk of pulmonary fibrosis [3, 10, 17].

Pharmacokinetic studies of bleomycin have shown a 45% urinary elimination over 3 days after continous infusion [24], with a close correlation to the creatinine clearance [6]. As creatinine clearance can be diminished after the administration of cisplatin the serum half-life of bleomycin might be prolonged when given according to the original Einhorn protocol, possibly resulting in a higher incidence of pulmonary fibrosis.

Because of this side effect, the Einhorn regimen was either no longer advised for infants and children [3] or only used for poor responders [14, 15, 26]. In the therapy regimen of the Children's Cancer Study Group, VBC was given at 9-week intervals, alternating with a regimen consisting of Adriamycin, actinomycin D and cyclophosphamide [1].

To avoid increased toxicity, the German Society of Pediatric Oncology decided in 1982 to modify the Einhorn protocol for non-seminomatous testicular [19] and non-testicular germ-cell tumors [17].

Patients and methods

Chemotherapy. Vinblastine (3 mg/m^2, days 1 and 2) is given i.v. push concomitant with bleomycin (15 mg/m^2, days 1–3) as continuous infusion. In addition, cisplatin (20 mg/m^2, days 4–8) is given with mannitol diuresis. According to a risk-stratified therapy, this combination (VBC) is given twice in testicular disease and four times in non-testicular mNSGCTs every 3 weeks; the cumulative bleomycin dose is limited to 180 mg/m^2. Additional chemotherapy is given to patients with poor prognosis, i.e. those with advanced testicular, ovarian and extragonadal germ-cell tumors.

The high effectiveness of VP-16 [4, 5, 8, 37] and ifosfamide [5, 29, 36] has been shown in relapsed patients. Hence, VP-16 is combined with cisplatin and ifosfamide as follows: VP-16 (100 mg/m^2, days 1–5), ifosfamide (1.5 g/m^2, days 1–5) with mesna uroprotection and cisplatin (20 mg/m^2, days 1–5) with mannitol diuresis. This additional chemotherapy (VPIC) is given following VBC twice in testicular cancer and four times in disseminated ovarian or extragonadal tumors every 3 weeks, with careful monitoring of blood counts and renal function.

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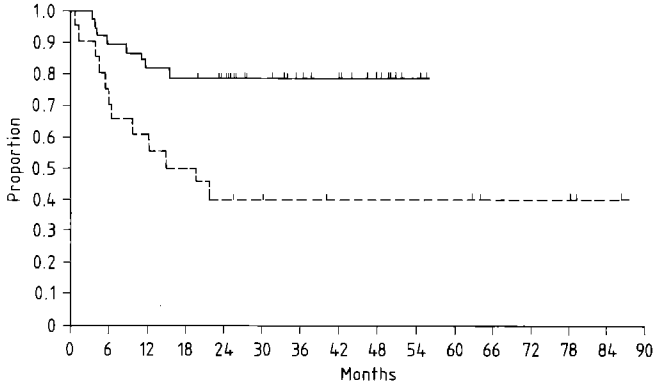

Fig. 1. Event-free survival of malignant extracranial non-testicular NSGCTs: protocol vs follow-up patients (MAKEI 83, status 10/87). ——— protocol patients; pts. = 8/37 failed; ----- follow-up patients; pts. = 12/20 failed; $P = 0.003$

Table 1. MAKEI 83 histology and tumor site of extracranial non-testicular germ-cell tumours

Site	Malignant NSGCT	(Dys) Germinoma	Teratoma
Ovarian	26	8	18
Sacrococcygeal	21	–	18
Retroperitoneal	1	2	2
Mediastinal	4	1	–
Vaginal	5	–	–
Cervical	–	–	1
Intestinal	–	–	1
Totals	57	11	40

Treatment strategy. In 1983 a pilot study for non-testicular germ-cell tumors was established and stratified according to histology, tumor site and tumor stage [17]. Diagnosis of mNSGCTs [i.e. yolk sac tumor (YST), embryonal carcinoma (EC), teratocarcinoma (TC), chorioncarcinoma (Ch) and mixed germ-cell tumors containing one or more of these entities] is obtained by histology after biopsy or tumor resection or clinically in advanced diseases by elevated tumor markers [AFP and/or β-human chorionic gonadotropin (β-hCG) levels of >1,000 ng/ml]. Ovarian tumors are staged according to the FIGO classification, and extragonadal primaries, according to soft-tissue sarcomas. Brain tumors are excluded.

Due to the relatively low incidence of mNSGCTs in infancy and childhood, patients are classified into two risk groups. The low-risk group includes ovarian tumors of FIGO stages Ia-Ic. Treatment consists of four courses of VBC. In ovarian tumors of stages Ib and Ic, if tumor markers decrease slowly after tumor resection, second-look surgery is carried out after four courses of VBC.

The high-risk group includes ovarian tumors of FIGO stages II–IV and all extragonadal primaries. After histological or clinical diagnosis, four courses of VBC are given, followed by second-look surgery or tumor resection. In sacrococcygeal germ-cell tumors, en bloc resection of the tumor and coccyx is mandatory.

Following surgery, four courses of VPIC are given. Due to the high cumulative dose of cisplatin and the increased myelotoxicity of VPIC, special guidelines for monitoring of blood levels and renal function are supplemented.

Table 2. MAKEI 83 relapses in malignant extracranial non-testicular NSGCTs according to histology

Histology	Protocol patients	Follow-up patients
Yolk sac tumor (YST)	4/25	4/9
Chorioncarcinoma (Ch)	0/1	–/–
Embryonal carcinoma (EC)	–/1	2/5
YST + EC/Ch	1/2	–/–
YST + Dysgerminoma	–/1	–/–
YST + Teratoma	1/6	5/5
>2 entities	–/1	1/1
Patients (*n*)	6/37	12/20

Table 3. MAKEI 83 relapses in malignant extracranial non-testicular NSGCTs according to tumour stage

Stage (TNM)	Protocol patients	Follow-up patients
T_1	3/20	2/6
T_2	2/15	6/7
T_3	1/1	3/5
M_1	–/1	1/2

Clinical data. Between January 1983 and December 1985, when the study was completed, 108 patients with different germ-cell tumors were registered. Protocol patients comprised 13 men/boys and 68 women/girls, compared with 4 male and 23 female follow-up patients. The age of the protocol patients ranged between 1 and 21 years, with a median age of 6 years; in follow-up patients the median age was 10 years (range, 1–19 years).

Information about histology and tumor site is given in Table 1. 57 patients with mNSGCTs were registered; the histology was reviewed by a panel of pathologists[1]. A total of 37 patients were treated according to the protocol. In 20 other patients, substantial differences in treatment were used including no chemotherapy after surgery (6), surgery in saccrococcygeal teratoma without resecting the coccygeal bone (4) or different chemotherapy (12).

Results

Event-free survival of protocol patients as estimated according to Kaplan and Meier [22] was 78%±6% at 57 months; the latest relapse occurred 16 months after diagnosis (Fig. 1). In follow-up patients the event-free survival was only 40%±10%; the latest relapse occurred 21 months after diagnosis.

In protocol patients the predominant histology was pure YST (Table 2), and in follow-up patients YST, YST combined with teratoma and embryonal carcinoma (EC). According to histology, most relapses occurred in patients

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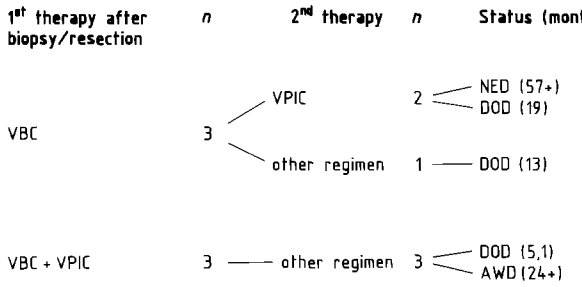

Fig. 2. Treatment results in protocol patients with relapses ($n = 6$) (MAKEI 83)

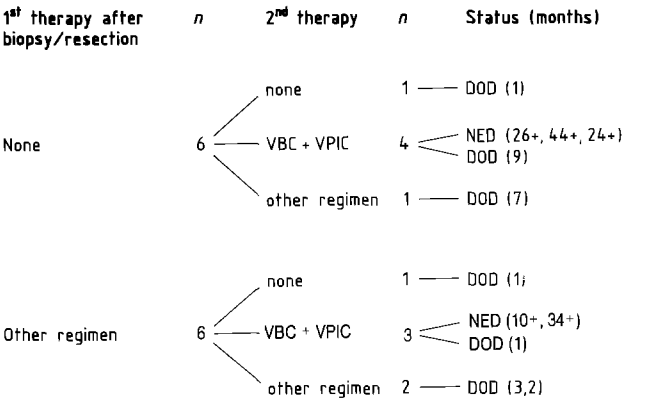

Fig. 3. Treatment results in follow-up patients with relapses ($n = 11$) (MAKEI 83)

with pure YST and YST combined with teratoma. The high incidence of relapses in follow-up patients with YST-teratoma is partly explained by insufficient surgery (coccyx not resected, 4 patients) and/or delayed chemotherapy due to inadequate initial diagnosis (teratoma only, 5 patients). According to these experiences, the relapse rates in both groups were independent of histology; however, the small number of cases must be taken into account.

The initial tumor stage (Table 3) happened to be lower in the protocol patients. The relapse rate was apparently independent of tumor stage. However, in follow-up patients the initial tumor stage seemed to be of prognostic value.

Reinduction therapy following relapse was established in 6/6 protocol patients (Fig. 2) and 10/12 follow-up patients (Fig. 3). Three ovarian stage I NSGCTs presented with relapse after VBC; one patient was salvaged by VPIC. None of the three patients who relapsed after VBC + VPIC remained disease-free after relapse therapy.

6 follow-up patients had initial surgery only and relapsed; 3/4 were salvaged by the MAKEI strategy with four courses of VBC, followed by second-look surgery and four courses of VPIC; 6/12 relapsed after initial surgery and chemotherapy consisting in most cases of VAC or a modified T-9 protocol; 2/3 relapsed patients were salvaged by VBC + VPIC.

Crude survival in protocol and follow-up patients (Fig. 4) was quite different from event-free survival, as 5/12 relapsed follow-up patients are now in second remission. The life-table analysis according to Kaplan and Meier [22] predicts an 83% ± 6% disease-free survival at 57 months for protocol patients and that of 54% ± 12% for follow-up patients.

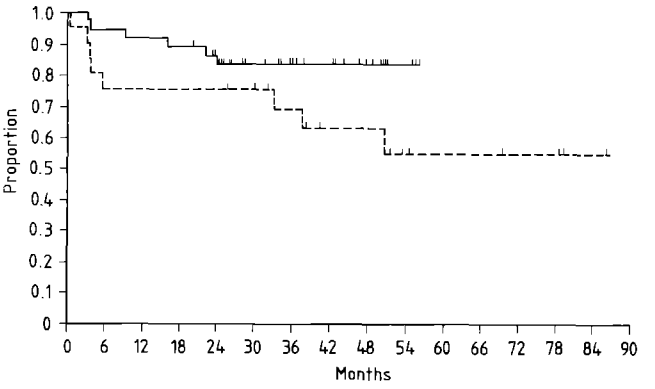

Fig. 4. Crude survival of malignant extracranial non-testicular NSGCTs: protocol vs follow-up patients (MAKEI 83, status 10/87). ——— protocol patients; pts. = 31/37 alive; – – – – – follow-up patients; pts. = 12/20 alive; $P = 0.09$

The toxicity of the treatment regimens is summarized in Table 4. Myelotoxicity was equal in both groups; one patient died during VBC and one died under treatment with VBC and VPIC. Cisplatin- and bleomycin-induced organ dysfunction was substantial and contributed to the high incidence of complications in patients treated with both regimens.

Discussion

In January 1983 the cooperative prospective trial for non-testicular germ-cell tumors was started, and 57 patients

Table 4. MAKEI 83 toxicity according to chemotherapy

	VBC	VBC + VPIC	Other regimen
Patients with chemotherapy	11 (100%)	32 (100%)	12 (100%)
Patients with complications	3 (27%)	7 (22%)	1 (8%)
Lethal septicemia	1 (9%)	1 (3%)	–
WBC $< 1.5 \times 10^9/l$	6	18	7
Platelets $< 50 \times 10^9/l$	5	16	6
Bone marrow depression (> 7 days)	1	1	1
Fever (> 38.5°)	3	8	3
Nephropathy	–	3	–
Neuropathy	–	2	–
Ototoxicity	–	2	–
Pneumopathy	2	1	–

with mNSGCTs were registered by December 1985. Due to the low incidence of mNSGCTs, the patients were divided into two risk groups according to the treatment anticipated, taking into account that histology, tumor site and tumor stage have been reported to be of prognostic value [2, 7, 9, 23, 27, 30, 32, 34].

In former studies of malignant germ-cell tumors, immature teratomas, dysgerminomas and mNSGCTs have been included [9, 30, 32]. With treatment regimens consisting of complete resection, irradiation and VAC chemotherapy, histology was proven to have prognostic value. Patients with YST, Ch and YST containing mixed germ-cell tumors had poorer relapse-free survival than those with the other histological entities.

A variety of different tumor sites and stages of NSGCTs are seen in infants and adolescents. Besides the testes, the ovaries and saccrococcygeal region are most often affected, followed by the mediastinum, the vagina and the retroperitoneum. Sacrococcygeal NSGCTs often relapse, despite rigorous treatment [27, 34]. Ovarian tumors that are localized have a better prognosis than those of FIGO stages III and IV [2]. Radical surgical therapy and intensive irradiation have been associated with long-term survival in extragonadal disease. In particular, Kohorn et al. [23] have summarized the histories of 23 infants with YST of the vagina, showing 9 long-term survivors, of whom only 2 did not undergo radical hysterectomy and vaginectomy but received multiagent chemotherapy and pelvic irradiation.

In spite of the well-known and promising results in testicular cancer patients, which Einhorn and Donohue first published in 1978, a therapy regimen other than VBC is often preferred in infants and children [7, 16, 26, 42]. To avoid the hazards of bleomycin toxicity and pulmonary fibrosis, VBC is considered to be a second-line treatment in infants and children with residual disease or relapses after therapy with VAC [10, 14, 26]. Otherwise, VBC is alternated with cycles of actinomycin D, cyclophosphamide and Adriamycin [1, 2] to lengthen the intervals between bleomycin courses.

The uncertainties involved in the treatment of mNSGCTs in infants and children are reflected in 20 follow-up patients whose treatment was different from that of the protocol patients. The relapse-free survival of this group was only $40\% \pm 10\%$, which could be increased to 54% by salvage therapy. These results are superior to those of the Children's Cancer Study Group, in which patients with similar histology and tumor sites are included [2].

Superior treatment results in children with malignant germ-cell tumors have recently been published. Flamant et al. [16] reported the results of 82 patients, including 20 with testicular cancer, treated with alternating courses of VAC and VBC, with a survival of 75%. It might be argued that the intervals between treatment courses used by these authors, which were shorter than those used in the protocol of the Children's Cancer Study Group [1], played a role in the improved survival, rather than the substition of Adriamycin for vincristine.

Mann et al. [26] summarized the treatment results in 52 children with mNSGCTs. 39 patients went into remission after high-dose VAC plus Adriamycin, VBC or bleomycin, etoposide and cisplatin, including salvage therapy. The range of these results is similar to that of our study, with $78\% \pm 6\%$ event-free survival and 83% crude survival. Preliminary results, including the main phase of the ongoing trial that was started in January 1986, have been reported elsewhere [18], showing an estimated event-free survival of $83\% \pm 5\%$ after 17 months.

Depending on the biological behaviour, survival in young boys with testicular mNSGCTs is $\geqslant 90\%$ [16, 26, 42]. From these results it must be concluded that a direct comparison of these studies with the trial MAKEI 83 is not possible.

Considering the risk factors, the main histology involved pure YST or YST in combination with other germ-cell tumors; therefore, no significant influence was detected in protocol patients. In addition, tumor site and tumor stage apparently had no prognostic value with this strategy. In particular, none of the children with mediastinal or retrovaginal primaries relapsed; all underwent delayed tumor resection, avoiding mutilating surgery.

A comparison of relapse rates in localized ovarian mNSGCTs of FIGO stages Ia–Ic with those in advanced ovarian and extragonadal tumors revealed no difference. These results show the importance of second-look surgery and additional chemotherapy with VPIC. One can assume that the regimen is very effective, as 3/5 pretreated patients were salvaged.

The toxicity of VBC and VPIC is remarkable, and intensive supportive care was required in about one-third of treated patients due to prolonged bone marrow depression. However, due to the supportive treatment guidelines, the chemotherapy-associated mortality was not increased in comparison with the mortality in patients treated with other regimens [15, 16, 26, 41].

Late effects such as mild pulmonary fibrosis, decreased creatinine clearance, hearing loss or slight disturbances of fine motor-coordination appeared in about half of the patients but are compatible with a normal life in every case. If protochemotherapy is given before surgery, tumor resection could be restricted to the site of origin, in most cases avoiding infertility or the excessive discomfort of major surgery.

Compared with those in adults, the results in children with ovarian mNSGCTs treated with VBC are superior [35, 38, 39] or identical [11, 40]. Adults with extragonadal mNSGCTs still have a grave prognosis, with survival of $< 50\%$ in spite of intensive cisplatin-based chemotherapy [12, 21, 25]. Whether the improved prognosis in younger patients is related to treatment incorporating both a cisplatin- and a VP-16/ifosfamide-based regimen or is simply due to a more chemosensitive histological entity in this age group remains unclear at present.

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