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Comparison of the rates of response to ifosfamide and cyclophosphamide in primary unresectable rhabdomyosarcomas

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Summary. In the 1981 cooperative soft-tissue sarcoma (CWS-81) study, a clear correlation between the degree of response to initial chemotherapy comprising vincristine, actinomycin D, cyclophosphamide, and Adriamycin (VACA) and the survival of patients with rhabdomyosarcoma was found. In the subsequent CWS-86 study, cyclophosphamide was replaced by ifosfamide (VAIA) in the expectation that the combination VAIA might be more effective than VACA. In both studies, the initial cytostatic response for primary unresectable tumors was evaluated after the first cycle of chemotherapy at weeks 7–9. The reduction in tumor volume was measured by computerized axial tomographic (CAT) scan or sonography, and the patients were categorized as complete responders, patients with a tumor regression of $>2/3$ albeit incomplete, patients with a tumor regression of $<2/3$ but $>1/3$, and nonresponders, who underwent either a tumor regression of $<1/3$ or tumor progression. We compared the response rate obtained with VACA chemotherapy and that resulting from VAIA chemotherapy. The preliminary data from this comparison show a tendency for a higher rate of good responders (complete and $>2/3$ tumor regression) to be induced by VAIA therapy (71%) than that obtained using the VACA combination (55%). From the response-prognosis relationship, we confidently expect that the final outcome for patients in the present study will be better than that in the previous study.

Introduction

In the 1981 cooperative soft-tissue sarcoma (CWS-81) study, a correlation between the degree of response after the first cycle of chemotherapy with VACA and the final outcome could be demonstrated in rhabdomyosarcoma (RMS) [2]. Patients undergoing a complete clinical response after 7–9 weeks of chemotherapy showed evidence of a disease-free survival (DFS) of 89%. Patients with a tumor reduction of $>2/3$ albeit incomplete had a DFS rate of 61%, and the group of patients undergoing a tumor reduction of $<2/3$ but $>1/3$ had a DFS rate of 31%; in the nonresponder group the DFS rate was 48%. The relapse pattern showed a greater incidence of metastasis in the group with a response of $<2/3$ than in the group with $>2/3$ tumor reduction.

These qualitative differences suggested a response-prognosis correlation induced by the initial cytostatic therapy. By means of single and multivariate analysis, we could show that this cytostatic time-response factor (CTRF) takes precedence over other well-known factors such as location, histological subtype, tumor size, and age [1]. Therefore, we decided to compare the initial rate of response in primary unresectable RMS patients given VAIA therapy with the rate of response in those given VACA therapy.

Patients and methods

The cytostatic combination of vincristine (VCR), actinomycin D (AMD), cyclophosphamide (C), and Adriamycin (ADR) – referred to as VACA – was used for the treatment of RMS in the first national, cooperative soft-tissue sarcoma study in the Federal Republic of Germany (CWS-81). The scheduling of this combination is shown in Fig. 1.

In the subsequent study (CWS-86), cyclophosphamide was replaced by ifosfamide in the expectation that the new combination – referred to as VAIA – would be more effective than VACA due to the introduction of ifosfamide (Fig. 2). Some data suggesting this probability existed in the literature [1, 2].

In both studies, the initial cytostatic response in primary unresectable rhabdomyosarcoma was evaluated after 7 weeks of exclusive chemotherapy. The reduction in tumor volume was measured by either CAT scan or sonography. The patients were categorized as follows: complete responders, patients with a tumor regression of $>2/3$ albeit incomplete, patients with a tumor reduction of between 2/3 and 1/3 in the original tumor volume, and nonresponders, who underwent either a tumor reduction of $<1/3$ or tumor progression.

Results

The response rate of 87 patients with primary unresectable tumor treated with VACA is shown in Table 1. Of 87 patients with stage III RMS, 13 (15%) were nonresponders. The remaining 74 patients (85%) responded with a tumor reduction of $>1/3$ within 7–9 weeks of chemotherapy. In

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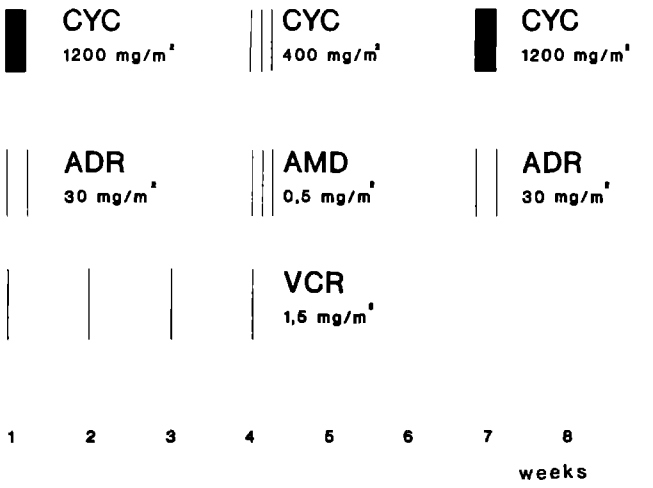

Fig. 1. Four-drug combination regimen given to patients in the CWS-81 study: vincristine (*VCR*), actinomycin D (*AMD*), cyclophosphamide (*CYC*), and Adriamycin (*ADR*) [VACA] were delivered to patients at the doses outlined in the diagram

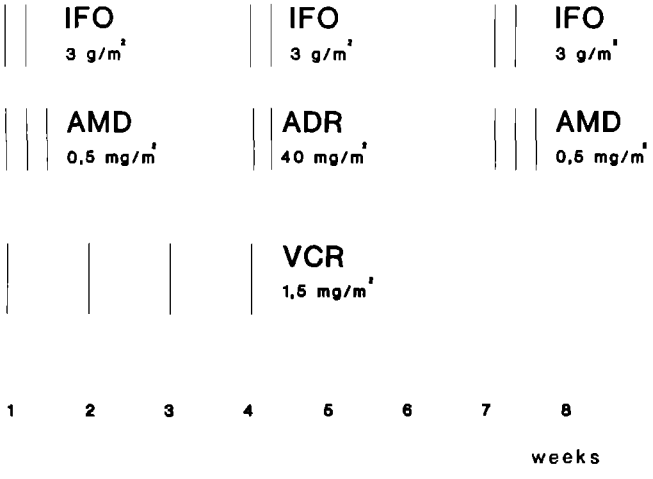

Fig. 2. Four-drug combination regimen, referred as VAIA, used for treatment in the subsequent CWS-86 study. The following drugs were given at doses outlined in the diagram: vincristine (*VCR*), actinomycin D (*AMD*), ifosfamide (*IFO*), and Adriamycin (*ADR*)

23 of 87 patients (26%), a complete clinical tumor reduction was achieved. A partial reduction of >2/3 of the tumor volume was achieved by 25 patients (29%), and 26 patients (30%) registered a reduction of between 1/3 and 2/3 in the original tumor size.

To date, 34 patients with primary unresectable RMS (stage III) have been registered in the CWS-86 study: 6 (18%) achieved a complete clinical remission, 18 (53%) had a tumor reduction of >2/3, 7 (20%) showed a tumor reduction of 1/3–2/3, and 3 (9%) were classified as nonresponders (Table 1). If one compares the response rates in the four groups after 7–9 weeks of VACA chemotherapy with those obtained with VAIA therapy, there seems to be a tendency for a higher rate of good responders (complete remission and tumor regression of >2/3) to be induced by VAIA therapy (71% with VAIA vs 55% with VACA; Table 1). Interestingly, the rate of complete responders is no higher in the group of patients receiving VAIA therapy than in those who underwent VACA therapy, and the nonresponder rate also does not seem to be reduced (15% nonresponder rate with VACA vs 9% with VAIA).

Table 1. Response to exclusive chemotherapy in patients with stage III RMS after 7–9 weeks

Response groups	Patients given (*n*)			Patients given (*n*)		
	VACA	(%)		VAIA	(%)	
Complete response	23	26	55[a]	6	18	71[a]
Tumor reduction of >2/3	25	29		18	53	
Tumor reduction of <2/3	26	30		7	20	
No response (<1/3)	13	15		3	9	
Totals	87			34		

[a] Good responders

Table 2. Tumor distribution by primary site, histology, and size

Category	CWS-81		CWS-86	
	Patients (*n*)	(%)	Patients (*n*)	(%)
Orbit	11	12	4	11
HxN	6	7	8	23.5
GU	19	22	8	23.5
Extremity	5	6	1	3
PM	28	32	8	23.5
Other	18	21	5	15.5
			$P = 0.19$	
Embryonal	69	79	23	68
Alveolar	14	16	7	20
Other	4	5	4	12
			$P = 0.26$	
<5 cm	31	36	16	47
>5 cm	48	55	18	53
No data	8	9	0	0
			$P = 0.59$	

No difference was evident in the distribution of the respective groups regarding tumor localization, size, and histology. The distribution of sites, histology, and size between the patients in the CWS-81 study and those in the CWS-86 study is listed in Table 2.

On the basis of the data thus far available, the advantage of the VAIA regimen lies in the higher number of responders with a tumor regression of >2/3. The difference in the rates of response to VACA and VAIA in this group is 24%.

Discussion

From the results it can be assumed that the higher response rate in patients with primary unresectable RMS given VAIA chemotherapy (71% vs 55% for those given VACA) is a result of the introduction of ifosfamide. Nevertheless, two points should be made:

1. The comparison is not based on a randomized study but is historical. As no significant differences were noted in the composition of the groups in terms of tumor histology, size, and site and because the measurement of the tumor

volume was terminal, the comparison nonetheless appears to be valid.

2. The combinations VACA and VAIA differ from each other in the total doses of Adriamycin and actinomycin D. The total dose of Adriamycin was reduced in the VAIA combination from 120 to 80 mg/m^2, with an increase from 30 to 40 mg/m^2 in the single Adriamycin dose. In the VAIA as opposed to the VACA combination, the total dose of actinomycin D was increased from 1.5 to 3 mg/m^2. As the effectiveness of Adriamycin is on a par with that of actinomycin D, the comparison between cyclophosphamide and ifosfamide appears to be justified.

On the basis of the prognostic evaluability of the early response to initial chemotherapy in the CWS-81 data, we expect better final results from the CWS-86 study in patients with stage III RMS.

References

1. Suder J, Stienen U, Kaatsch P, Harms D, Schmidt D, Spaar H-J, Treuner J (1986) Analyse prognostischer Faktoren beim Rhabdomyosarkom; Vorläufige univariate und multivariate Ergebnisse der Cooperativen Weichteilsarkomstudie (CWS-81). Klin Paediatr 198: 218–223
2. Treuner J, Kaatsch P, Anger Y, Seipp A, Spaar H-J, Gerein V, Suder J, Niethammer D (1986) Ergebnisse der Behandlung von Rhabdomyosarkomen (RMS) bei Kindern. Ein Bericht der Cooperativen Weichteilsarkomstudie (CWS-81) der Gesellschaft für Pädiatrische Onkologie. Klin Paediatr 198: 208–217