doi:10.4149/neo_2009_03_215

Prognostic factors in patients with relapsed or primary refractory germ cell tumors

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Received November 11, 2008

The aim of the study was to define prognostic factors of overall and event- free survival in patients with germ cell tumors progressing after platinum-based induction chemotherapy with or without surgery. A total of 98 progressing patients were identified out of 700 patients with germ cell tumors treated with platinum-based induction chemotherapy in National Cancer Institute in Bratislava with or without surgery. 98 progressing patients received first salvage chemotherapy from October 1986 to November 2007 due to progression after a previous partial or complete response to induction chemotherapy as well as patients who failed to achieve favourable response to primary therapy. Prognostic factors of survival and event-free survival after first salvage chemotherapy were assessed by univariate analysis. For all 98 progressing patients the median time from the start of induction chemotherapy to progression was 10,2 months (range: 0-256,7 months). 24 (24 %) patients relapsed after 2 years. Median overall survival time following progression was 25,4 months. Estimated 2- and 5- year overall survival rate for all progressing patients was 46 % (95 % CI 41-61%) and 24 % (95% CI 31-51%) respectively. Survival after first salvage chemotherapy was significantly enhanced for patients with age more than 40 years at primary diagnosis, nonvisceral metastasis at the time of induction chemotherapy, prior CR to induction chemotherapy, progression-free interval > 2 years, serum human chorionic gonadotropin level at relapse above or bellow 100 IU/l, a normal serum lactate dehydrogenase level at relapse, one site of metastasis at relapse, treatment with cisplatin-based first salvage chemotherapy, first regimen VIP and favourable response to salvage chemotherapy. Estimated 2- and 5-year event-free survival rate for all patients was 30% (95% CI 24-43%) and 16%(95% CI 19-37%) respectively. As a significant favourable prognostic factors of event-free survival were identified: prior CR to induction chemotherapy, progression-free interval > 2 years, one site of metastasis at relapse, treatment with cisplatin-based first salvage chemotherapy, first line salvage regimen VIP and favourable response to salvage chemotherapy. Identification of prognostic features in patients with germ cell tumors progressing after platinum-based induction chemotherapy may direct salvage therapy and requires further investigation of new combination of salvage therapy for those with poor prognosis. Our study showed the indispensable revaluating of chemosenzitivity in patients with late relapses and therapeutic value of additive surgical approach after salvage chemotherapy in patients with reccurent germ cell tumors.

Key words: germ cell tumor, relapse, progression, prognostic factor, cisplatin-based chemotherapy, salvage

Germ cell tumors, represents model of successful, highly treatable malignancy, even in advanced disease, with curability rate from 70 to 80 %. Despite all successes in induction treatment of advanced germ cell tumors, 20 to 30 % patients relapse after some time or don't achieve response to standard induction platinum-based chemotherapy [0]. Both groups of patients need effective salvage treatment. Nowadays there are 3 opportunities in salvage regimens: conventional-dose chemotherapy, high-dose chemotherapy and new experimental agents. Additive surgical approach after salvage chemotherapy is necessary component of complete intervention. Conventional-dose salvage chemotherapy is standard therapy for recurrent germ cell tumors, because randomised trials did not approve high-dose chemotherapy as a better approach so far [0, 0]. Long-term survival for

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patients with relapsed or platinum-refractory germ cell tumors is unsatisfying, range from 30 to 40 %. Identifying reliable prognostic features in patients with relapsed or platinum-refractory gem cell tumors may direct salvage therapy and could improve survival rate for these patients. Few studies were trying to identify prognostic factors in patients with recurrent germ cell tumors [0, 0, 0, 0, 0]. Cardinal Fossa's et al study identified 3 independent prognostic parameters in patients with recurrent germ cell tumors. Based on this study, Sammler et al evaluated the impact of determined prognostic factors in patients with germ-cell tumors relapsing or progressing after cisplatin-based first-line chemotherapy. They suggested a clinical benefit for patients with poor prognosis features receiving high-dose chemotherapy [0] . The aim of our study was to establish prognostic factors of overall and event-free survival in patients with relapsed or primary refractory germ cell tumors which may help to determine patients with poor prognosis, considering them as candidates for high-dose chemotherapy or clinical trials in the future.

Table 1. Patients characteristics at the time of diagnosis and induction chemotherapy

Patients characteristics at the time of induction chemotherapy		
Category	**Number of patients**	**%**
Age (in years)	**98**	**100**
Median	36	/
Range	19 – 62	/
Age subgroups (in years)	**98**	**100**
<30	34	35
30-39	34	35
40-49	27	28
>=50	3	3
Prognostic group (IGCCCG)	**95**	**100**
"good risk"	44	46
"intermediate risk"	15	16
"poor risk"	36	38
Primary tumor site	**98**	**100**
Testis	86	88
Extragonadal	12	12
Retroperitoneal	5	5
Mediastinal	6	6
Gl. Pinealis	1	1
Histology	**98**	**100**
Mixed/Nonseminoma	84	86
Seminoma	13	13
Unknown	1	1
Metastatic extent of disease at induction chemotherapy	**98**	**100**
No visceral metastasis	38	39
With visceral metastasis	60	61
Induction chemotherapy	**98**	**100**
BEP/ EP	56	57
Other	42	43
Number of courses of induction chemotherapy	**98**	**100**
2-31	0	10
4	51	52
5-6	32	33
>6	5	5
Response to induction treatment	**98**	**100**
CR	38	39
PRnm-	43	44
IR (PRnm+)	13	13
PGR	4	4

Patients and methods

Total of 98 progressing patients were identified out of more than 700 patients with germ cell tumors treated with platinum-based induction chemotherapy in our centre with or without surgery. Our study represents an analysis of patients who progressed during or following platinum-based induction chemotherapy. This includes patients who never achieved a response (primary refractory) and those with new disease activity after achieving a complete or partial response to induction chemotherapy.

All patients were treated with platinum-based induction chemotherapy between November 1980 and April 2007. 5 patients belonged to stage I.A at the time of diagnosis (without lymph or visceral metastases). These patients received induction chemotherapy at the time of 1.relapse. Due to this we evaluated metastatic extent of disease at the time of start of induction chemotherapy in all patients. Patients with operable residual post-chemotherapy masses underwent surgery to remove them.

All patients in the study received both induction and first salvage chemotherapy. However, 5 patients relapsed in retroperitoneum but they did not receive first salvage chemotherapy at the time of that first relapse, 4 patients underwent complete retroperitoneal lyphadenectomy (RPLA) and 1 patient received radiotherapy to retroperitoneum extra muros. Those patients received first salvage chemotherapy at the time of second relapse in our centre (we evaluated their characteristics at the time of second relapse prior to first salvage chemotherapy).

Histological subtyping of the primary germ cell tumor was based on the Mostofi and Sesterhenn adaptation of Dixon/ Moore classification [0].

Complete response to therapy (CR) was defined as clinical and radiological absence of all tumor manifestations (including normalization of serum alpha fetoprotein (AFP) and human chorionic gonadotropin (hCG), or complete resection of residual mature teratoma or necrotic/fibrotic tumor tissue. Incomplete response to therapy (IR=PRnm+) was defined as radiological decrease of malignant disease more than 50% with persistently elevated tumor markers (without serially rising values) or histological findings of residual cancer in resection specimen. Stabilisation (SD) was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progression. Partial remission marker negative (PRnm-) comprised patients with residual tumor masses with normal level of serum tumor

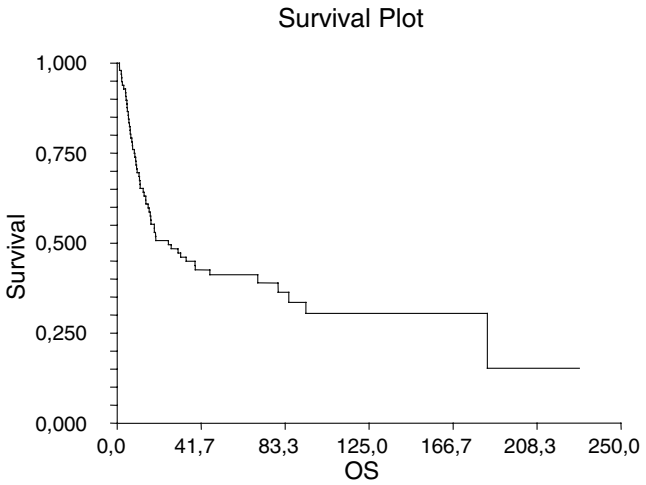

Figure 1. Kaplan-Meier curve of overall survival after first salvage chemotherapy

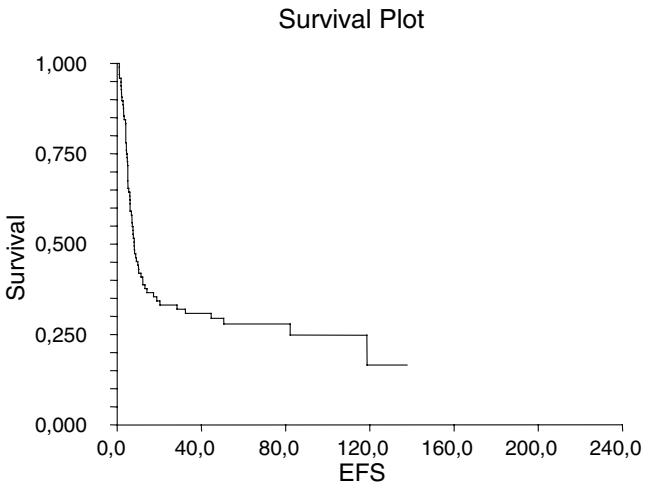

Figure 2. Kaplan-Meier curve of event-free survival after first salvage chemotherapy

markers. Progression (PGR) was defined as development of new metastases and/or clearly rising level of serum tumor markers.

Prognostic factors of survival from the date of progression were identified. Potential prognostic factors included patient characteristics at initial diagnosis and induction chemotherapy, response to induction chemotherapy, duration of progression free-interval, patient characteristics at relapse, salvage regimen, response to salvage regimen and surgical intervention after first salvage regimen (Table 1, Table 3).

Time to progression was measured from the date of start of induction chemotherapy to the date of relapse or progression.

Overall survival time was measured from the date of diagnosis of progression to the date of death or date last seen.

Event-free survival was measured from the start of first salvage chemotherapy to the date of relapse or progression, or the date of death or date last seen.

In the final analysis patients with missing data on any factor were excluded case by case.

Survival distributions were estimated by Kaplan-Meier method and survival curves were compared using logrank test.

Results

Ninety eight patients with germ cell tumors relapsed. Of these, 59 (60 %) have died and the median follow-up time of those still alive is 57,5 months (1,7-226,3 months).

Primary tumor site was in testes in 86 (88 %) of our patients. 44 (46 %) patients belonged to the good, 15 (16 %)

Table 2. Induction regimens

Induction regimens			
Induction regimen	**Number of patients**	**Induction regimen**	**Number of patients**
BEP	56	HD-VIP	4
BEP + VIP	2	HD-VIP+TIP	1
BEP + VeIP	1	T-BEP+OxaliPt	1
BEP + ADR, IFO, VP-16, cDDP	2	PVB	2
BEP + Bleo, IFO, ADR, cDDP	1	PVB + VBL, VP-16, ADR, cDDP	2
CCNU, Farmorubicin, CFA, MTX + BEP	1	PVB + VBL, VP-16, ADR, cDDP, Bleo	1
T-BEP	13	TIP	1
EP	5	CBDCA	1
VIP	3	cDDP+VBL	1

BEP: Bleomycin, Etoposide, Cisplatin; VIP: Etoposide, Ifosfamide, Cisplatin, VeIP: Vinblastine, Ifosfamide, Cisplatin; ADR: Adriamycine; IFO: Ifosfamide; VP-16: Etoposide; cDDP: Cisplatin; Bleo: Bleomycin; CCNU: Lomustine; CFA: Cyclophosphamide; MTX: Metothrexate; T-BEP: Paclitaxel, Bleomycin, Etoposide, Cisplatin; EP: Etoposide, Cisplatin; HD: high dose; PVB: Vinblastine, Etoposide, Cisplatin; OxaliPt: Oxaliplatin; CBDCA: Carboplatin, VBL: Vinblastine

Table 3. Patients characteristics at relapse

Patients characteristics at relapse		
Parameter	**Number of patients**	**%**
Time from start of induction therapy to progression (months)	**98**	**100**
<6	18	18
6 – 12	39	40
13 – 24	17	17
24 – 36	6	6
>36	18	19
hCG at relapse (IU/l)	**97**	**100**
Normal	54	56
<100	14	14
100 – 1000	16	16
>1000	13	13
AFP at relapse (kIU/l)	**98**	**100**
Normal	48	49
<100	18	18
100->1000	22	22
>1000	10	10
LDH at relapse (ng/ml)	**91**	**100**
Normal	29	32
Elevated	62	68
Sites of relapse (1)	**98**	**100**
Markers only	6	6
Abdominal lymph nodes (LN)	29	30
Mediastinal/neck LN +/- previous LN	7	7
Lung metastasis +/- all previous LU	30	31
Other visceral metastasis (+- previous)	26	27
Sites of relapse (2)	**98**	**100**
No lung or other visceral metastasis	42	43
Lung or other visceral metastasis	56	57
Number of metastatic sites at relapse	**98**	**100**
1	55	56
≥2	43	44
Cisplatin-based first salvage regimen	**98**	**100**
Yes	89	91
No	9	21
First salvage regimens	**98**	**100**
TIP	38	39
VIP	27	28
HD-VIP	8	8
GCP	9	9
Other	16	16
Response to first salvage treatment	**95**	**100**
CR	24	25
PR nm-	38	40
SD	7	7
PR nm+ (IR)	8	9
PGR	18	19
Surgery after first salvage chemotherapy (RPLA/ metastasectomy)	**98**	
No	80	82
Complete resection	8	8
Incomplete resection	9	10

patients to intermediate and 36 (38 %) to poor risk group as defined by IGCCCG prognostic classification at the time of diagnosis (3 patients could not be classified) [0].

The median time to progression from start of induction chemotherapy was 10,2 months (range: 0-256,7 months) for all patients. 4/98 (4 %) patients progressed within 4 weeks after completion of induction chemotherapy (primary refractory patients). 24/98 (24 %) patients progressed after more than 2 years after completion of induction chemotherapy, whereas all of them achieved favourable response to induction chemotherapy (13 patients CR, 11 patients PRnm-).

Median survival time following progression was 25,4 months and the estimated 2- and 5-year survival was 46 % (95% CI 41-61%) and 24 % (95% CI 31-51%).

Patients characteristics at the time of induction chemotherapy are described in Table 1.

The majority of patients (52%) received four courses of induction chemotherapy. 56 (57 %) patients received combination chemotherapy BEP/EP.

Details of induction regimens are described in Table 2.

Twenty nine (30 %) of patients underwent RPLA after induction chemotherapy, whereas complete resection was in 16 (55 %) cases and incomplete resection of necrotic/fibrotic tissue or mature teratoma in 13 (45 %). 1 patient refused RPLA after induction chemotherapy. 8 (8 %) patients underwent metastasectomy in other locations, while complete resection of pulmonary metastases was achieved in 4 cases, in 2 patients complete resection of mediastinal masses and in last 2 patients just incomplete resection of mediastinal masses was achieved. None of residual masses removed by surgery demonstrated viable residual cancer.

Detailed data on patients characteristics at relapse are described in Table 3.

First salvage chemotherapy was given between October 1986 and November 2007. In 98 patients a variety of first salvage regimens were employed, while 89 patients received platinum-based first salvage regimens. 9 patients received HD-chemotherapy. Details of first salvage regimens gives Table 4.

17 (17%) patients underwent additive surgical approach after first salvage chemotherapy, whereas complete resection was in 8 (47%) cases and incomplete resection of necrotic/fibrotic tissue or mature teratoma in 9 (53%).

Univariate analysis of prognostic factors of overall survival after first salvage chemotherapy identified these significant prognostic factors of overall survival after first salvage chemotherapy: “age”, “metastatic extent of disease at induction chemotherapy”, “response to induction chemotherapy”, “time from start of induction chemotherapy to progression”, “hCG at relapse”, “LDH at relapse”, “number of metastatic sites at relapse”, “first salvage chemotherapy” and “response to first salvage chemotherapy”.

“Age” was an important prognostic factor of survival, p = 0,0227, patients older than 40 years had enhanced survival compared to younger patients at the time of diagnosis.

“Prior response to induction chemotherapy” was an important predictor of survival after first salvage chemotherapy, p = <0,0001. 38 (39 %) patients with CR to

Table 4. Salvage regimens

Salvage regimens			
1. line salvage regimen	**Number of patients**	**1. line salvage regimen**	**Number of patients**
TIP	38	VIP	27
GCP	9	HD-VIP	8
HD-CAV + HD-VIP	1	Act.D	2
COMF	2	VBL, CFA, 5-FU+MTX, ADR, VP-16	1
Epirubicine+DTIC+IFO	1	Epirubicine+cDDP	1
SU	1	BEP	1
VeIP	1	VeIP + EP	1
VBL, ADR, MTX, CaLV	1	5-FU, CaLV	1
VBL,CFA, Act.D, 5-FU + MTX, ADR, VP-16	1		

HD-CAV: high dose Cyclophosphamide, Adriamycine, Vincristine; COMF: Cyclophosphamide, Vincristine, Methotrexate, 5-Fluorouracile; DTIC: Dacarbasine; SU: Sutent; Act.D: Actinomycin D; 5-FU: 5-Fluorouracile; CaLV: Leucovorine; BEP: Bleomycin, Etoposide, Cisplatin; VIP: Etoposide, Ifosfamide, Cisplatin, VeIP: Vinblastine, Ifosfamide, Cisplatin; ADR: Adriamycine; IFO: Ifosfamide; VP-16: Etoposide; cDDP: Cisplatin; Bleo: Bleomycin; CFA: Cyclophosphamide; MTX: Methotrexate; EP: Etoposide, Cisplatin; HD-high dose; PVB: Vinblastine, Etoposide, Cisplatin; VBL: Vinblastine; TIP: Paclitaxel, Ifosfamide, Cisplatin

induction chemotherapy had enhanced survival, with a median survival time of 31,6 months (1,1-229,4 months), compared to 43 (44 %) patients with PRnm-, with a median survival time of 18,4 months (1,2-183,7 months), 13 (13 %) patients with PRnm+, with a median survival time of 9,6 months (2,1-67,0 months) and 4 (4 %) patients with PGR, with a median survival time of 2,4 months (2,2-7,6 months).

Seventy four (76 %) of patients, with "progression from start of induction chemotherapy" less than 24 months had significantly adverse prognosis, with a median survival time 18,4 months (1,2 – 229,4 months) compared to 24 (24 %) patients with "progression from start of induction chemotherapy" more than 24 months, with a median survival time 183,7 months (1,1 – 183,7), p = 0,0471. 18/24 (75%) patients relapsed after more then 3 years from start of induction chemotherapy, with median time to progression 71,0 months (range 38,6-260,7 months) and have reached the best survival whitin the whole group of our patients with a median survival time 183,7 months (2-year survival of 72 %).

Level of "hCG at relapse" significantly influenced prognosis, p = 0,0302, but level of "AFP" was not significant predictor of survival, although a trend towards inferior survival was shown in patients with elevated AFP at relapse, p = 0,2080.

"LDH at relapse" was a significant prognostic factor of survival, p = 0,0223. 51 (58 %) patients with normal level of LDH at relapse had enhanced prognosis, with a median time of survival 38,7 months, compared to 38 (42 %) patients with elevated level of LDH, with a median time of survival 19,1 months.

"Number of metastatic sites at relapse" influenced survival, patients with 2 or more sites of metastases had adverse survival, p = 0,0095.

"Cisplatin-based first salvage chemotherapy" significantly influenced prognosis, patients without cisplatin in first salvage regimen had an inferior survival, p = 0,0148.

Twenty seven patients with "first salvage regimen VIP" had enhanced prognosis, with median survival time of 37,1 months (2-year survival rate of 70%) compared to 38 patients with TIP, with median survival time of 31,5 months (2-year survival rate of 42%). Concurrently, patients with first salvage regimen VIP had enhanced prognosis compared to all patients with any other first salvage regimen, p = 0,0063.

"Response to first salvage chemotherapy" was an important predictor of survival, p = <0,0001. 24 (25 %) patients with CR to first salvage chemotherapy had enhanced survival, with a median survival time of 183,7 months, compared to 38 (40 %) patients with PRnm-, with a median survival time of 13,3 months, 8 (8 %) patients with PRnm+, with a median survival time of 8,8 months and 18 (19 %) patients with PGR, with a median survival time of 4,3 months.

Eight (8%) patients, who underwent complete additive surgical approach of residual disease after first salvage chemotherapy had enhanced survival, with median survival time of 79,9 months (2-year survival of 75%), compared to 9 (10%) patients with incomplete additive surgery, with a median survival time of 16,4 months (2-year survival of 33%) and 80 (82%) unoperated patients, with a median survival time of 25,4 months (2-year survival of 45%) .

Table 5 gives results of the univariate analysis of survival after first salvage chemotherapy.

Univariate analysis of prognostic factors of event-free survival after first salvage chemotherapy:Univariate analysis identified these significant prognostic factors of event-free survival after first salvage chemotherapy: "time from start of induction chemotherapy to progression", "response to induction treatment", "number of metastatic sites at relapse", "first

Table 5. Results of univariate analysis of survival and event-free survival after first salvage chemotherapy

Results of univariate analysis of survival and event-free survival after first salvage chemotherapy							
	Number of patients	Median survival (in months)		2-year survival (%)		Log-rank P-value	
		OS	EFS	OS	EFS	OS	EFS
Age (in years)						**0,0227**	**0,0059**
<30	34	11,1	6,1	24	9		
30-39	34	18,4	7,6	44	32		
40-49	24	85,2	82,2	70	52		
50> 3	69,8	20,3	100	33			
Prognostic group (IGCCCG)						0,0776	0,1260
„good risk“	44	46,0	13,2	57	39		
„intermediate risk“	15	16,4	6,8	27	14		
„poor risk“	36	11,1	5,0	39	22		
Primary tumor site						0,5287	0,7890
Testis	86	26,8	8,2	47	29		
Extragonadal	12	9,3	4,1	42	33		
Histology						0,0570	0,1093
Seminoma	13	44,8	12,2	62	38		
Mixed/ nonseminoma	84	19,1	7,6	44	29		
Metastatic extent of disease at induction chemotherapy						**0,0456**	**0,0094**
No visceral metastasis	38	69,8	14,1	58	45		
With visceral metastasis	60	15,4	6,1	38	20		
Induction chemotherapy						0,5980	0,2398
BEP/ EP	56	30,2	8,8	48	33		
Other	42	16,6	7,5	43	26		
Number of courses of induction chemotherapy						0,6064	0,1856
2-3	10	69,8	44,6	60	60		
4	51	34,2	8,2	45	30		
5-6	32	16,6	7,1	41	19		
>6	5	79,9	17,3	60	40		
Response to induction treatment						**<0,0001**	**<0,0001**
CR	38	69,8	10,2	58	42		
PRnm-	43	30,2	8,2	49	29		
IR (PRnm+)	13	9,6	5,0	15	8		
PGR	4	2,3	1,0	0	0		
Time to progression (months)						**0,0471**	**0,0112**
<= 24	74	18,4	7,1	42	23		
> 24	24	183,7	32,4	58	50		
hCG at relapse (IU/l)						**0,0302**	0,1028
< 100	68	34,2	10,1	51	34		
>= 100	29	12,9	6,1	31	21		
AFP at relapse (kIU/l)						0,2080	0,5409
< 100	55	34,2	8,2	53	35		
>= 100	43	16,7	7,5	37	23		
LDH at relapse (ng/ml)						**0,0223**	0,2323
Normal	51	38,7	8,2	51	33		
Elevated	38	11,4	7,1	32	22		
Sites of relapse (1)						0,3985	0,3160
Markers only	6	8,8	4,5	50	17		
Abdominal lymph nodes (LN)	29	31,5	18,8	55	38		
Mediastinal/neck LN +/- previous LN	7	93,6	28,4	71	57		
Lung metastasis +/- all previous LU	30	18,4	6,1	43	20		
Other visceral metastasis (+- previous)	26	14,2	6,1	31	28		
Sites of relapse (2)						0,1412	0,0932
No lung or other visceral metastasis	42	46,0	14,1	57	38		
Lung or other visceral metastasis	56	16,6	6,1	38	24		
Number of metastatic sites at relapse						**0,0095**	**0,0429**
1	55	69,8	12,2	58	36		
≥2	43	14,2	6,1	30	21		

Table 5. continued

Cisplatin-based first salvage regimen						**0,0148**	**<0,0001**
Yes	89	30,2	9,1	48	33		
No	9	6,8	3,1	22	0		
First salvage regimens						**0,0063**	**0,0019**
VIP	27	37,1	16,2	70	48		
TIP	38	31,5	8,1	42	29		
HD-VIP	9	16,7	5,1	33	13		
GCP	8	14,3	7,7	38	25		
Other	16	6,8	4,1	25	13		
First salvage regimens						0,6455	0,9231
Conventional-dose	89	30,2	8,1	46	31		
High-dose	9	18,5	7,7	44	22		
Response to first salvage treatment						**<0,0001**	**<0,0001**
CR	24	183,7	118,7	75	58		
PRnm-	38	31,5	10,2	55	32		
SD	7	13,3	5,0	29	13		
PRnm+ (IR)	8	8,8	2,3	13	6		
PGR	18	4,3	7,1	17	14		
Response to first salvage treatment						**<0,0001**	**<0,0001**
Favourable	62	79,9	17,3	63	42		
Nonfavourable	33	9,3	4,1	18	9		
Surgery after first salvage chemotherapy (RPLA/ metastasectomy)						0,4837	0,7207
No	80	25,4	8,2	45	30		
Complete resection	8	79,9	8,1	50	38		
Incomplete resection	9	16,4	7,2	33	22		

salvage chemotherapy" and "response to first salvage chemotherapy".

Table 5 gives results of the univariate analysis of event-free survival after first salvage chemotherapy.

Discussion

Progression after induction chemotherapy was observed in 98 patients with germ cell tumors. 76 (796%) patients relapsed within 24 months and 24 (24 %) patients after 24 months after induction chemotherapy (11/24 (46 %) patients after 60 months) which indicates the necessity to continue regular follow up in patients with germ cell tumors for the rest of their lives.

Our analysis concentrates mostly on prognostic features evaluable before first salvage chemotherapy. The overall estimated long-term survival was 24 %, which is comparable to other reports [0, 0, 0, 0, 0].

Fossa et al, determined in the multivariate analysis 3 independent prognostic factors of survival in patients with germ cell tumors progressing after platinum-based induction chemotherapy: "progression free interval", "response to induction chemotherapy" and "level of serum human chorionic gonadotropin (hCG) and alpha fetoprotein (AFP) at relapse", which were identical to our findings, except the "level of AFP at relapse", which was not a significant prognostic factor of survival for patients in our study [0].

Gerl et al and Josefsen et al, defined "complete response to induction chemotherapy" as an independent positive prognostic factor of survival in patients with refractory or relapsed germ cell malignancy after conventional-dose cisplatin-based salvage chemotherapy, which was confirmed by our study [0, 0].

Motzer et al identified significantly enhanced survival and/or response to salvage chemotherapy in patients with prior CR to induction chemotherapy, treatment with cis-platin based salvage regimen, a testis primary site, a normal human chorionic gonadotropin level, a normal serum lactate dehydrogenase level, one site of metastasis, and particularly poor survival in patients with prior incomplete response to induction chemotherapy. All prognostic factors of survival for relapsing patients identified in this study correspond also to our findings. Despite testis primary site was not a significant prognostic factor of survival in our group of patients, a trend towards inferior survival was shown in patients with extragonadal primary site [0].

Nichols et al, determined as the most powerful prognostic parameter of survival for relapsing patients after CR to induction chemotherapy "long time to progression after induction chemotherapy" which was confirmed by our study as well [0].

Study of Baniel et al, emphasized the fundamental role of surgery in patients with late relapse. Salvage chemotherapy was limitedly effective in patients progressing after 2 years from start of induction chemotherapy in their study [0]. In contrast, our results in patients with late relapse (24 patients, with a median time to progression 49,2 months) point out the

role of salvage chemotherapy in these patients, because 16/24 patients had favourable response to first salvage regimen (10 patients CR, 6 patients PRnm-) and additive surgical approach underwent just 2 out of these patients. 18/24 (75%) patients relapsed after more then 3 years from start of induction chemotherapy, and interestingly they have reached the best survival whitin the whole group of our patients (2-year survival of 72 %). All of them achieved favourable response to induction chemotherapy (10 patients CR, 8 patients PRnm-) and 14 (78%) of them favourable response to first salvage chemotherapy (9 patients CR, 5 patients PRnm-) consecutively. Despite late relapses generally considered as chemorefractory, cases of these patients with median time to progression 71,0 months (range 38,6-260,7 months) refer to noticeable sensitivity to salvage chemotherapy in these patients.

We tried to evaluate the importance of additive surgical approach after salvage chemotherapy in our study as well. Despite finding out an enhanced overall survival in patients with complete resection of residual disease after first salvage chemotherapy, 8 patients with a median time of survival 79,9 months compared to 9 patients with incomplete surgery, with a median time of survival 16,4 months and 80 unoperated patients, with a median time of survival 25,4 months, demonstrated event-free survival was similar in these three groups of patients, with a median time of event-free survival 8,1 months, 7,2 months and 8,2 months respectively. The manifest discrepancy between overall and event-free survival is hard to interpret. It is not evident, if an enhanced overall survival in 8 patients with complete additive surgical approach is caused by biological characteristics of their malignant disease or due to given surgery, since 6 of them relapsed after first salvage treatment again, while 1 patient only in retroperitoneum after prior complete RPLA, 2 patients in lungs after prior complete pulmonary metastasectomy, 1 patient in lungs and mediastinum after prior complete pulmonary metastasectomy and 2 patients in other locations (retroperitoneum and CNS) after prior complete pulmonary metastasectomy after first salvage chemotherapy.

Horwich et al, referred to interesting fact in their study. Elevated tumor markers at the time of progression in patients with late relapse were not an adverse factor of survival, this was the case when the progression period was short. 11/24 (46 %) patients with late relapse in our study had elevated AFP, 3/24 (13%) patients hCG and 1 (4 %) patient had elevated both tumor markers at relapse, while these patients achieved 2-year survival in 58 %, with median time of survival 38,8 months, which supported these findings as well [0].

In summary, about 20-30 % of patients with advanced germ cell tumors are not cured by standard induction chemotherapy and require effective salvage treatment. Demonstrated long-term survival of our patients warrants the need to continue investigation of more effective salvage therapy. Prognostic features in patients with recurrent germ cell tumors evaluable before salvage therapy may direct the subsequent salvage treatment. Our study showed the indispensable evaluation of chemosenzitivity in patients with late relapses and therapeutic value of additive surgical approach after salvage chemotherapy in patients with reccurent germ cell tumors.

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