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Efficacy of a Toxicity-Adjusted Topotecan Therapy in Recurrent Small-Cell Lung Cancer

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Abstract: A prospective multi-center trial investigated whether topotecan given at a starting dose of 1.25 mg/m^2 with individual dose adjustment can improve safety in patients with relapsed/refractory SCLC without loss of efficacy.

Patients received topotecan intravenously on days 1–5 every 21 days up to 6 courses. In the absence of relevant hematotoxicities topotecan was escalated to 1.5 mg/m² and reduced to 1.0 mg/m² in case of severe hematotoxicities.

Of 170 recruited patients 73.2% had stage IV disease, 63.4% had platinum containing pre-treatment. Patients received a total of 521 courses. In 72.6% of those courses the dose remained at 1.25 mg/m²; in 9.1% it was reduced and in 18.3% escalated. Overall response rate was 14.1% including one complete response, 28.8% had stable disease. Median duration of response was 13.6 weeks, median survival 23.4 weeks. Clinical benefit was obvious for sensitive as well as for refractory patients. Hematotoxicity of grade 3 or 4 was clearly lower compared to standard dose of 1.5 mg/m².

In conclusion, topotecan in a dose of 1.25 mg/m² appears to be as effective as the dose of 1.5 mg/m² with reduced toxicity. Since patients with recurrent SCLC have a poor prognosis they especially benefit from the good tolerability.

Keywords: second-line therapy, small cell lung cancer, topotecan

INTRODUCTION

Small cell lung cancer (SCLC) is considered to be among the most chemo-sensitive solid tumours [1]. With combination chemotherapy, such as platinum/etoposide or cyclophosphamide/doxorubicin/etoposide, objective response rates of 20% to 90% are observed, with a median survival of about 10 months. However, the majority of patients will experience tumour recurrence after successful therapy [2,3,4]. The prognosis with second line treatment was analyzed by Huisman et al. from 21 published phase II studies including 1749 patients showing response rates of 20% [5]. Response to a second line therapy most likely depends on response to first-line treatment and length of treatment-free interval. Patients developing disease progression within three months after first-line therapy are classified as refractory. Patients with disease progression more than 3 months after last treatment of first line therapy, which has induced an objective response, are classified as sensitive [3]. Since refractory patients have a smaller chance to respond to any drug than sensitive patients, stratification between sensitive and refractory patients is necessary to describe the efficacy of a tested regimen. Topotecan is a specific inhibitor of the nuclear enzyme topoisomerase I which interferes with DNA replication and transcription. Inhibition of this enzyme produces lethal DNA damage [6]. Topotecan was reported to be effective in second line treatment of SCLC [7]. In a randomized phase III study topotecan (1.5 mg/m² IV days 1-5 every 21 days) was at least as effective as the three-drug regimen CAV (cyclophosphamide 1000 mg/m², doxorubicin 45 mg/m² and vincristine 2 mg). Response rate was 24.3% in the topotecan arm and 18.3% in the CAV arm. Median survival was 25.0 weeks for topotecan and 24.7 weeks for CAV. This study demonstrated that topotecan has significant advantages in controlling disease related symptoms [8]. In three studies a

total of 264 evaluable patients with recurrent SCLC were stratified as either refractory (126 patients) or sensitive (138 patients) according to their response to first-line therapy. All patients received topotecan 1.5 mg/m² day 1-5 intravenously every 21 days. The efficacy is summarized in Table 1 [9,10,11]. The most frequent adverse event of the 1.5 mg/m²/day regimen in all studies is neutropenia grade 3/4: von Pawel et al. reported an incidence of grade 4 neutropenia of 67.3% of patients (32.5% of courses) in the phase II study [12] and 70.2% (38.7% of courses) of patients in the phase III study [8]. Ardizzoni et al. [11] reported grade 4 neutropenia in 46.9% of courses. Grade 4 thrombocytopenia occurred in 8 – 11% of courses [11,12]. Infection associated with grade 4 neutropenia occurred in 28% of patients and 8.7% of courses and 4 treatment related deaths were reported (3.7% of patients) in the topotecan arm of the comparative phase III trial [8]. Ardizzoni et al. observed infection in 6 % of courses and one treatment related death [11]. Perez Soler et al. reported a lower incidence of haematological toxicity when topotecan was administered in a dose of 1.25 mg/m² days 1-5 IV in patients with SCLC refractory to etoposide/platinum. In 28% of courses grade 4 neutropenia was observed, there were no episodes of neutropenic fever and no treatment related deaths [13].

The objective of this multi-center phase II trial was to evaluate prospectively the efficacy and safety of topotecan starting with a starting dose of 1.25 mg/m² and with dose adjustment in accordance with toxicity. Patients with recurrent or refractory SCLC were stratified according to pre-treatment with platinum-containing or platinum-free regimen and response to pre-treatment.

PATIENTS AND METHODS

Patient Eligibility

Patients with histologically and/or cytologically documented SCLC, who have recurred or progressed after first-line chemotherapy, were eligible. Further inclusion criteria were: bi-dimensional measurable disease (minimum size of lesion had to be 2 x 2 cm) male or female patients 18-75 years old; ECOG performance status $\leq$ 2; written informed consent according to the local institutional ethics committee requirements; leukocyte count $\geq$ 4000/μL; platelet count $\geq$ 100,000/μL; haemoglobin concentration $\geq$9.0 g/dl and creatinine clearance $\geq$60 mL/min.

Exclusion criteria included: Pre-treatment with a topoisomerase I inhibitor; more than one pre-treatment; pregnant or lactating women; history of neoplasm other than SCLC; serious concomitant medical conditions; dementia; surgery within 2 weeks before study entry; participation in any other clinical study within 30 days before study entry.

The study was approved by ethical committee of each participating centre.

Descriptive statistical methods were used to assess response evaluation, dose intensity, time to progression and toxicity data. Survival estimates were performed according to Kaplan-Meier.

Treatment

Topotecan (Hycamtin®, GlaxoSmithKline) was administered as a 30-minute intravenous (IV) infusion at a starting dose of 1.25 mg/m² for 5 consecutive days,

repeated every 21 days for six cycles. One topotecan dose escalation of 0.25 mg/m² was to be performed in cycle 2 in the absence of haematological toxicities grade 3 or 4. Further dose escalations of 0.25 mg/m² in the absence of haematological toxicities grade 3 or 4 was left to the discretion of the investigator.

Topotecan dose reduction of 0.25 mg/m² was to be performed in case of grade 4 neutropenia lasting 7 days or longer, or complicated by fever or infection; platelet count < 25000/μL; or neutrophil count < 1500/μL, and platelet count < 100000/μL on day 22, and in case of grade 3 or 4 non-haematological toxicity (except for nausea, vomiting and alopecia). In any case the minimum topotecan dose had to be 1.0 mg/m²/d. No dose re-escalation was allowed.

Use of granulocyte colony-stimulating factor (G-CSF) was left to the discretion of the investigator. Duration of the treatment was based on response evaluation which was performed after a minimum of two courses. In case of complete response, treatment was continued for two additional courses. In case of partial response, or stable disease treatment was continued until disease progression or severe toxicity was observed or for the planned treatment of 6 cycles. Patients were withdrawn from study in case of disease progression or incomplete haematological recovery two weeks after scheduled treatment or for generally accepted reasons. Response and toxicity were evaluated according to WHO and NCI-CTC criteria (revised version 94-Dec-21) [14].

Study Design

The objectives of the study were to evaluate response rates, response duration, toxicities, dose-intensity, and median survival of relapsed small cell lung cancer

treated with topotecan in a starting dose of 1.25 mg/m^2/day. Patients were stratified according to pre-treatment with platinum or not, and according to response to pre-treatment (sensitive versus refractory).

According to given treatment, patients were grouped to a “safety”, “survival” or “response” collective. The objectives of the study were analyzed within the corresponding group: Patients (n=170) who received at least one dose of study drug were evaluable for safety analysis. Patients (n=164) who had received at least one course of study medication and did not show any serious study deviation (i.e. no measurable disease) were evaluable for survival, demographic data, dose intensity, and time to progression. Objective response evaluation was performed in patients (n=120) who received at least two courses of study drug and had a tumour baseline status with re-evaluation (response collective). In 41 patients clinical progressive disease or death was observed prior to response re-evaluation after the end of cycle 2. Clinical progressive disease, death or missing response data were regarded as progressive disease, according to a worst-case scenario (intention-to-treat).

Tumour response is presented as judged by the centre, median time to progression and survival were calculated according to the Kaplan-Meier product limit method.

RESULTS

Patient Characteristics

170 patients were enrolled from 44 participating centers between February 1998 and June 1999. Last follow-up was performed in December 2002. All patients were evaluable for safety analysis. 164 patients were evaluable for survival analysis (2 patients did not complete a full course, 4 patients did not have a bi-dimensionally measurable lesion). Tumour response as the primary endpoint of the study, was evaluated in all patients, who at least received one dose of study drug (n=170, intention-to-treat). 37 patients received less than 2 courses; 7 patients were lost to follow up. 76.8% of patients had performance status ECOG 0-1. The majority of patients (73.2%) had distant metastatic disease. 63.4% of patients had received a platinum-based primary therapy. The overall response rate to primary therapy was 76.8%. 34.8% of patients were refractory, whereas 65.2% of patients were sensitive to prior therapy. The median time to progression after first line therapy was 191 days (Table 2).

Dosing

164 patients received a total of 514 topotecan courses. 22.6% of patients (n=37) received only 1 course of therapy and 2.4% (n=4) of patients received 8 courses. 52 patients (31.7%) received 2 courses. Cycle 1 was administered to 164 patients and cycle 6 to 36 patients. In 58.2% of courses (n=299) the starting dose was maintained. The topotecan dose had to be reduced to 1.0 mg/m²/d in 8.9% (n=46) of courses. The targeted dose of topotecan (1.5 mg/m²/d) was reached in 32.9% (n=169) of courses. In the first course the topotecan dose was administered as a starting dose of 1.25 mg/m²/d to 98.2% of patients (n = 161). This starting dose was maintained in 46.5% of patients (n=59) in course 2. Dose escalation to 1.5 mg/m²/d topotecan was

performed in 37.8% of patients (n=48), whereas in 15.7% (n=20) it was reduced to 1.0 mg/m²/d. Protocol deviations according to dose modification in cycle 2 was noticed in 13,1% (no dose-escalation to 1.5 mg/m2) and 17.0% (no dose-reduction to 1.0 mg/m2) of patients, respectively. While the number of patients who received subsequent courses decreased, the percentage of patients who received an escalated dose rose from 46.7% (cycle 3) to 58.3% (cycle 6). At the same time, the percentage of patients who received a reduced dose decreased from cycle 3 (13.3%) to cycle 6 (8.3%) with the exception of cycle 5 (14.0%). The percentage of patients within cycle 3-6 receiving the starting dose was between 30.2% (cycle 5) and 40.0% (cycle 3). Median dose intensity of all administered cycles was 1.25 mg/m²/d (Table 3).

Efficacy

Response to treatment

170 patients were evaluated for response (intention-to-treat). The overall response rate was 14.1% with one complete response and 23 (13.5%) partial responses. Stable disease was observed in 25.9% and progressive disease in 60.0% of patients. No difference in response rates was seen between patients with or without platinum-containing pre-treatment with overall response rates of 14.9% and 12.7%, respectively. However, patients who had been refractory to primary therapy achieved a lower response rate and a higher rate of disease stabilization to topotecan therapy. The overall response rate was 8.6% in refractory patients versus 17.1% in sensitive patients, stable disease was observed in 36.2% and 20.7% of patients, respectively (Table 4). Among all responding patients the median time to response was 7.2 weeks

(range 2.9-14.7). There was no significant difference between patients with platinum-containing and platinum-free pre-treatment 8.1 versus 6.6 weeks (p = .8952), respectively. In refractory patients time to response was significantly longer: 12.4 weeks versus 6.4 weeks (p = .0260). As shown in Table 5, median duration of response was 13.6 weeks (range 3.0-47.9) and was not significantly different among the sub-groups. Median time to progression of all patients was 8.0 (range 0.1-53.6) weeks. An analysis according to stratification parameters shows no significant differences between sensitive versus refractory patients.

Survival

164 patients were evaluable for survival. The median survival time was 23.4 weeks (95% CI 19.0-27.0 weeks. range 0.9-92.4 weeks) and mean survival was 28.3 weeks (Fig. 1). Median survival time for patients with CR and PR, SD, or PD was 43.4 weeks, 28.6 weeks, and 26.0 weeks respectively. Stratified according to pre-treatment and response to pre-treatment no differences in median survival time could be detected. Median survival time of 62 weeks was found in patients with objective response to topotecan and non-platinum-containing pre-treatment.

After one year 25 patients were alive according to a one-year survival rate of 15.2%.

Toxicity

170 patients received at least one dose of topotecan and were evaluable for toxicity. Treatment delays of more than 14 days due to haematological toxicity were observed in 5 patients. Delays of more than 7 days due to toxicity or management reasons were performed in 11.7% of courses. Therapy had to be stopped in 9 patients. All cases were associated with myelosupression. One treatment related death was observed. This patient with poor performance status declined hospitalization despite grade 4 neutropenia and thrombocytopenia. Major side effects were neutropenia and leukopenia whereas anaemia and thrombocytopenia were less common. Grade 3 and 4 neutropenia occurred in 27.7% and 27.6% of patients and in 31.5% and 6.9% of treatment courses, respectively. Granulocyte colony-stimulating factor was administered in 21.2% of patients in 11.5% of treatment courses. Febrile neutropenia was observed in 0.8% of courses. The incidence of grade 3 and 4 thrombocytopenia was 10.3% and 5.0% of treatment courses (23.5% and 13.5% of patients),

respectively. 10% of patients received a platelet substitution in 3.3% of treatment courses. Anaemia grade 3 and 4 was less common (5.5% and 0.6% of all courses), in 3.6% of courses erythrocytes had to be substituted. No evidence of cumulative haematological toxicity was observed. Haematological toxicity among the subgroups is presented in table 6 demonstrating lower rates of neutropenia and thrombocytopenia in refractory patients. In patients without platinum-containing pre-treatment grade 3 and 4 anaemia was more frequent. Non-haematological toxicities of grade 3 and 4 which were observed in more than 1% of patients were: pain 5.9%, infection 4.7%, nausea 1.8% and fever 1.8%.

DISCUSSION

Despite the high chemosensitivity of SCLC, the majority of patients have a relapse after induction chemotherapy. The prognosis of patients with recurrent disease remains poor. The goals of chemotherapy in this patient population are to obtain maximum control of disease symptoms, prevent serious complications and increase survival without diminishing quality of life [1,4,5]. The current prospective study is the first trial in which an individual dose adjustment with a reduced topotecan starting dose is evaluated in order to reduce toxicity, a procedure which is in close relationship to the clinical practice in relapsed SCLC.

A prospective analysis of the haematological toxicity profile of topotecan, administered at a dose of 1.25 mg/m²/d on days 1-5 to pre-treated patients with ovarian cancer revealed, that the severity of topotecan-induced thrombocytopenia is maximal at the first cycle, but significantly decreases from the second cycle without dose reductions [15]. Fields et al. performed a retrospective analysis of second line

patients with SCLC treated with the standard topotecan dose. In 110 patients the dose was reduced to $\leq$ 1.25 mg/m^2/d due to haematological toxicity. Response rates and survival in the reduced dose population were similar to the results of the standard dose population [16].

Our results are demonstrating that treatment with the reduced topotecan starting dose of 1.25 mg/m²/d and an individual dose adjustment is equi-effective to the efficacy of the standard dose of 1.5 mg/m²/d. Von Pawel et al. reported a median survival of 25 weeks for 98 patients receiving the IV regimen of 1.5 mg/m²/d in the phase II and 107 patients in the phase III study, in our study the median survival is 23.4 weeks. Of note, in these trials mostly sensitive patients had been included [8,12].

The better tolerability of this regimen is also reflected in a reduced rate of haematological toxicities compared to recently reported trials where was given as a standard dose. In the current trial grade 4 neutropenia and thrombocytopenia occurred in 6.9% and 5% of courses, respectively and febrile neutropenia was observed in only 0.8%. In other studies with standard dose IV topotecan in relapsed SCLC grade 4 neutropenia and thrombocytopenia were observed in 32.5% to 46.9% and 7.7% to 11.9% of courses [8,11]. Febrile neutropenia occurred in 3.3% to 6% of IV T courses. Non-haematological toxicities were mild and did not influence patients' well-being. Notably grade 3 and 4 neutropenia and thrombocytopenia is less frequent in refractory compared to sensitive patients. This is very important for refractory patients, since the clinical benefit seems not to be associated with a higher toxicity and justifies a therapy in this special patient group.

Median dose intensity of all administered cycles was 1.25 mg/m²/d. In 58.2% of all courses the starting dose was maintained and in 32.9% of courses the dose was escalated to 1.5 mg/m²/d. Only 8.9% of courses had to be reduced due to haematological toxicity compared to phase II studies with a standard topotecan dosage, where dose reductions of 16 to 19% were reported [11,12].

The overall response rate of 14.1% obtained in this study is comparable to recently published reports using IV topotecan in the standard dosage (Table 1). As expected, the response rate was higher in sensitive patients (17.1%) than in refractory patients (8.6%) and median time to response was longer for refractory patients (12.4 weeks) than for sensitive patients (6.4 weeks). This is in accordance with reports of Ardizzoni et al. and Perze-Soler et al. [11,13]. On the other hand, no difference was seen between patients with or without platinum containing pre-treatment indicating the lack of cross resistance to platinum. Perez-Soler et al. reported responses with topotecan in etoposide-refractory patients and concluded that it may overcome etoposide resistance [13]. Interestingly in 36.2% of refractory patients and 20.7% of sensitive patients stabilization of disease could be observed. As shown by Cesano et al. stable disease (SD) represents a potential clinical benefit, since SD has the same survival benefit as partial response (PR) versus progressive disease (PD) [17]. Primary progression rate also provides support for a clinical benefit: it shows no difference between the four subgroups and is not higher in refractory patients.

Median duration of response was 13.6 weeks and median time to progression was 8.0 weeks for all patients. Patients with platinum-free pre-treatment had an advantage in median time to progression compared to patients with platinum-

containing pre-treatment. Median time to progression was 9.6 weeks versus 7.9 weeks in these groups (Table 5). The results concerning pre-treatment are difficult to compare with other studies, because the distinction between platinum-containing and platinum-free pre-treatment is not reported.

The median survival was 23.4 weeks and one-year survival was 15.2% without any differences between the subgroups. The survival data for all patients are comparable to reports using the standard topotecan dosage in phase II and III trials. [9,10,11]. Ardizzoni et al. [11] reported longer survival data for sensitive patients than for refractory (6.9 versus 4.7 months). In our study survival data of refractory patients are similar to survival in sensitive patients (23.7 versus 22.4 weeks). High rate of disease stabilization, especially in the refractory patients group may contribute to better median survival of refractory patients in our study. This is in agreement with previous reports in which survival of patients with PR was comparable to survival of SD patients following topotecan therapy of SCLC and ovarian cancer [17]. Stable disease is a valid endpoint provided that symptom palliation is achieved and treatment related toxic side effects are mild.

A meta-analysis of four multi-center trials treating patients with relapsed SCLC with topotecan at a starting dose of 1.5 mg/m²/d suggests that dose reductions due to haematological toxicity ($\leq$ 1.25 mg/m²/day) are not in correlation with decreased efficacy. The response rate in the reduced dose population was 17.3% and median survival 29.9 weeks compared to 18.1% and 28.6 weeks in the standard dose population. The results support our results indicating that moderate topotecan dose reductions could counterbalance the haematological toxicity and are not associated with reduced efficacy [16].

To our knowledge this is the first prospective trial in relapsed SCLC which shows a positive impact on safety parameters of a topotecan therapy in a reduced starting dose with an individual dose adjustment. It is of special interest that this impact is in association with the same efficacy compared to standard topotecan regimens. These results demonstrate that patients with sensitive and refractory relapsed SCLC can benefit from chemotherapy and that treatment related side effects are manageable by individual dose titration.

Table 1. Efficacy of IV topotecan (1.5 mg/m²/d, days 1-5) in second-line SCLC

Author	N (evaluable)	CR	PR	OR (%)	SD (%)	Median survival (weeks)
Eckhardt J et al. 1996 [9]	38 R* 36 S** 74	- 3	1 4	2.6 19.4 10.8	45 36 40.5	20.4 26.6 n.r.
Ardizzoni et al. 1997 [11]	47 R* 45 S** 92	1 6	2 11	6.4 37.8 21.7	40 31 35.9	18.8 27.6 21.6
von Pawel et al. 1997 [10]	41 R* 57 S** 98	- 1	1 7	2.4 14.0 9.2	n.r. n.r. 27	16.3 25.7 21.6

* R: Patients who failed to respond or progressed within 90 days of first-line therapy were termed refractory

** S: Patients who relapsed after 90 days after first-line therapy were termed sensitive

n.r.: not reported

Table 2: Patients characteristics

	No.	%
Patients registered	170	100
Assessable for response (intention to treat)	170	100
Assessable for survival	164	96.5
Assessable for toxicity	170	100
Age (years)		
Median = 61 years		
< 60	66	40.3
≥ 60	98	59.7
Sex		
Male	128	78.0
Female	36	22.0
ECOG performance status		
0 (Karnofsky 100%)	34	20.7
1 (Karnofsky 80-90%)	92	56.1
2 (Karnofsky 60-70%)	37	22.6
Extent of disease		
Limited disease	4	2.4
Extensive disease without distant metastasis	38	23.2
Extensive disease with distant metastasis	120	73.2
No data	2	1.2
Liver metastases		
Present	59	36.0
Absent	105	64.0
Brain metastases		
Present	46	28
Absent	118	72
Best response to first-line treatment		
Complete Response	31	18.9
Partial Response	95	57.9
Stable Disease	9	5.5
Progression	29	17.7
Time to relapse after first-line therapy		
< 3 months (refractory)	57	34.8
≥ 3 months to < 6 months (sensitive)	107	65.2
Time to progression after first-line therapy		
Median, days	191	
Prior anticancer treatment		
Prior radiotherapy	85	51.8
Prior surgery	17	10.4
First-line therapy		
Platinum-based	104	63.4
Non-platinum-based	60	36.6
First-line chemotherapy regimen		
Carboplatin/etoposide/vincristin	48	29.3
Platinum (cisplatin or carboplatin) /etoposide	36	21.9
Carboplatin/taxol/etoposide	7	4.3
Adriamycin/cyclophosphamide/vincristine	20	12.2
Epirubicin/cyclophosphamide/vincristine	20	12.2
Cyclophosphamide/etoposide/adriamycin	12	7.3
Other regimes	21	
Number of measurable lesions		
1	69	42.1
2	50	30.5
3	33	20.1
>3	12	7.2

Table 3. Dose intensity and administered courses

Course	Administered dose in courses							
	1.00 mg/m²		1.25 mg/m²		1.5 mg/m²		> 1.5 mg/m²	
	n	%	n	%	n	%	n	%
1	2	1.2	161	98.2	1	0.6	0	0.0
2	20	15.7	59	46.5	48	37.8	1	0.8
3	10	13.3	30	40.0	35	46.7	1	1.3
4	5	8.2	22	36.1	34	55.7	2	3.3
5	6	14.0	13	30.2	22	55.8	2	4.7
6	3	8.3	12	33.3	21	58.3	1	2.8
7	0	0.0	1	25.0	3	75.0	0	0.0
8	0	0.0	1	25.0	3	75.0	0	0.0

Table 4. Responses according to stratification (percent of patients)

	All patients n = 170	Platinum pre-treatment		Response to pre-treatment*	
		Yes n = 107	No n = 63	Sensitive n = 111	Refractory n = 58
Complete response	0.6	0.9	0.0	0.9	0.0
Partial response	13.5	14.0	12.7	16.2	8.6
Overall response	**14.1**	**14.9**	**12.7**	**17.1**	**8.6**
Stable disease	25.9	25.2	27.0	20.7	36.2
Progressive disease	60.0	59.8	60.3	62.2	55.2
95% CI for response		30.8-50.1%	27.6-52.8%	28.8-47.5%	31.7-58.5%

* missing data (n=1)

Table 5. Response duration, time to progression and survival

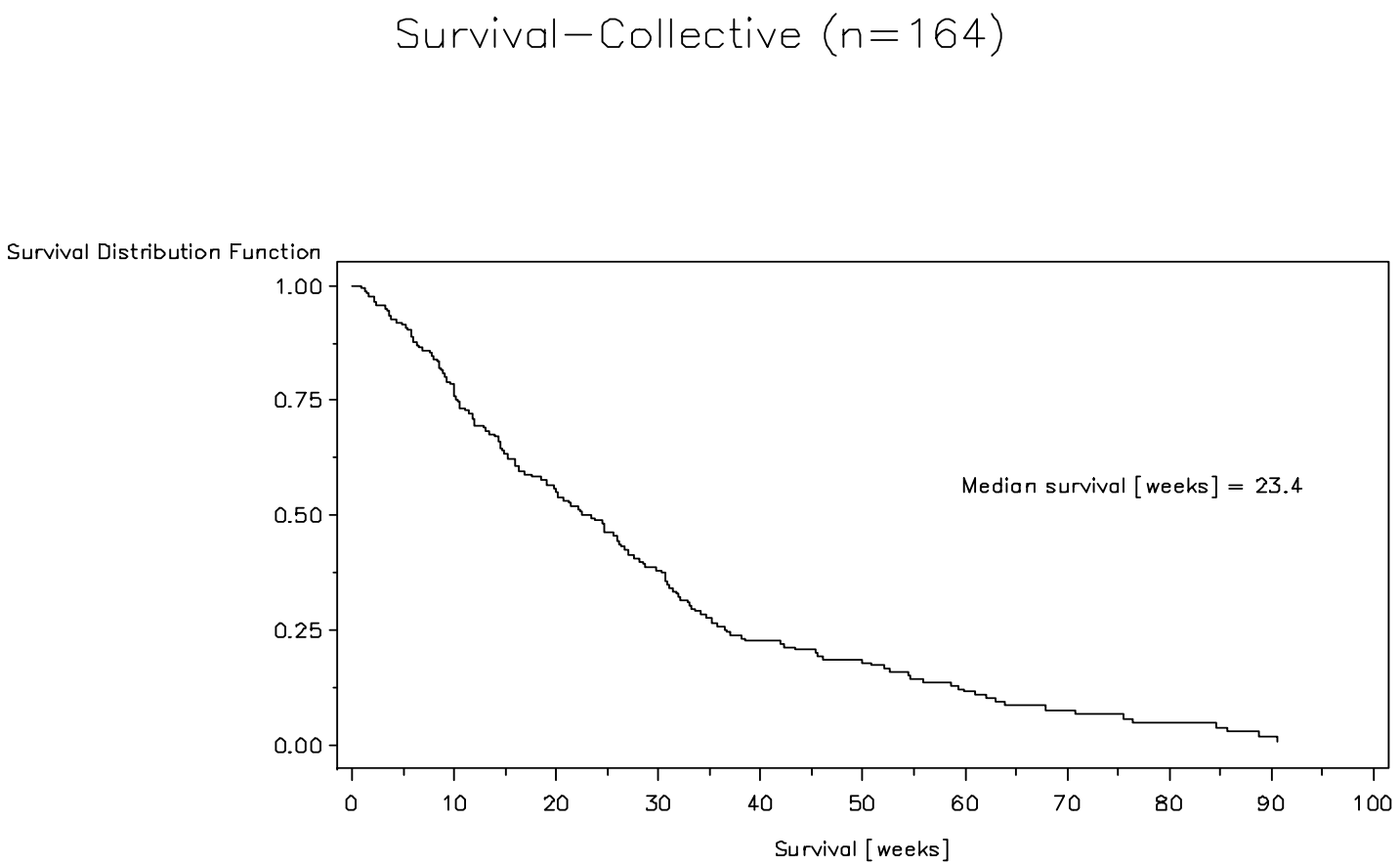
	Patients	Median (weeks)	Range	p
Response duration				
All	24	13.6	3.0-47.9	
Platinum + PT	16	12.1	3.0-47.9	0.3718
Platinum - PT	8	19.4	7.3-40.9	
Sensitive	19	15.0	3.0-47.9	0.3393
Refractory	5	13.0	4.7-27.1	
Time to progression				
All	164	8.0	0.1-53.6	
Platinum + PT	104	7.9	2.1-53.6	0.0173
Platinum - PT	60	9.6	0.1-48.0	
Sensitive	107	8.0	2.1-53.6	0.4720
Refractory	57	9.6	0.1-41.3	
Survival				
All	164	23.4	0.9-92.4	
Platinum + PT	104	23.4	0.9-92.4	0.8776
Platinum - PT	60	22.9	1.1-83.1	
Sensitive	107	22.4	0.9-92.4	0.8199
Refractory	57	23.7	1.1-85.7	

Platinum + PT = Platinum containing pre-treatment
Platinum – PT = Platinum free pre-treatment

Table 6. Haematological toxicity grade 3/4 (% patients)

	All n = 170 G3 / G4	Platinum pre-treatment		Response to pre-treatment	
		Yes n = 104 G3 / G4	No n = 60 G3 / G4	Sensitive n = 107 G3 / G4	Refractory n = 57 G3 / G4
Leukopenia	44.1 / 17.6	44.3 / 16.3	45.5 / 21.2	47.7 / 22.4	38.6 / 10.5
Neutropenia	27.7 / 27.6	28.9 / 31.7	38.4 / 23.3	35.6 / 31.7	26.3 / 22.8
Thrombopenia	23.5 / 13.5	25.0 / 12.5	20.1 / 16.6	12.2 / 16.8	15.8 / 8.8
Anaemia	16.0 / 1.7	14.4 / 1.9	18.4 / 1.6	14.0 / 2.8	19.3 / 0

Figure 1. Kaplan-Meier plot: overall survival



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