Topotecan in the treatment of relapsed small cell lung cancer

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Abstract: Small cell lung cancer (SCLC) represents about 15% to 20% of all lung cancers. Chemotherapy is the cornerstone of the treatment, cisplatin–etoposide combination being the most used combination as first-line therapy. Despite high initial chemosensitivity, most SCLC patients will experience relapse sooner or later. Unfortunately, second-line chemotherapy does not result in a high response rate like first-line therapy, most patients having developed wide chemoresistance. This chemoresistance is far more important in refractory patients, ie, those who never responded to first-line therapy or who relapsed within 3 months after the end of chemotherapy, than in sensitive patients, ie, those who relapse more than 3 months after the end of chemotherapy. Topotecan, a topoisomerase I inhibitor, is the most studied drug in this second-line setting and has proved its efficacy as a single agent and in combination. A phase III trial comparing oral topotecan to best supportive care (BSC) in relapsed SCLC demonstrated a significant survival benefit as well as a better quality of life. Although the usual schedule is 1.5 mg/m^2, days 1–5 intravenously, it is not convenient for patients with relapsed SCLC, especially those who are refractory because of their short survival expectation. Oral topotecan is of similar efficacy and much more convenient with limited stay in a treatment unit and has a comparable toxicity profile for these patients with short expected survival. Combination of topotecan with platinum salts or taxanes does not seem to improve further the outcome of the patients and thus single-agent therapy with topotecan is the standard treatment for relapsed SCLC.

Keywords: topotecan, small cell lung cancer, chemoresistance

Introduction

Small cell lung cancer (SCLC) is a highly chemosensitive tumor but, unfortunately, not chemocurable. After a response rate of about 80%, sooner or later most of the patients will relapse, especially those with extensive disease stage (ED) at diagnosis. Response to second-line therapy is a rare event and eventually most patients who relapse die of their disease within a few weeks. However, among the population of patients who experience recurrence of their disease there are characteristics that will affect the probability of response to second-line therapy. Thus, it is very important to classify these patients, especially in a clinical trial setting, in order to make proper comparisons between drugs.

Topotecan is a topoisomerase I inhibitor which was first developed for ovarian cancer and recurrent SCLC and has been the most studied drug for the latter indication.

Outcome of SCLC patients under treatment

Whenever extensive work-up is performed, with modern imaging procedures, at least two-thirds of the patients have ED at diagnosis, meaning that tumor and connections cannot be included within a radiation therapy port.

Standard treatment of SCLC is based on chemotherapy, mainly the cisplatin – etoposide combination which has been shown to be the best (Sundstrom et al 2002).

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A third or even a fourth drug may be added for PS 0-1 patients with better results at the expense of increased toxicity (Pujol et al 2001). In cases of limited disease stage (LD), radiation therapy is given concomitantly with chemotherapy or on an early alternating schedule, with a significant survival benefit compared to chemotherapy alone (Warde and Payne 1992). In patients with ED, thoracic radiation therapy is not indicated. In LD, prophylactic cranial irradiation is indicated in cases of complete response (Auperin et al 1999). Recently, prophylactic cranial irradiation has also been discussed for ED patients who achieve response to induction treatment (Slotman et al 2007).

Median survival time is highly dependent on the extent of disease. In LD, median survival time is around 18 months with a 2-year survival rate of 33% to 40% and a 5-year survival rate of about 10%, whereas in ED, median survival time is around 10 to 12 months with almost no survival at 2 years. These figures have not been modified recently even though a 2-month median survival improvement has been shown in clinical trials over 20 years, an improvement that parallels the introduction of cisplatin (Chute et al 1999). Modifying the drugs provides no improvement in survival: the better results of cisplatin – irinotecan compared to cisplatin – etoposide observed in Japanese patients were not confirmed in European and North American patients (Hanna et al 2006). Administration of very high doses of chemotherapy supported by transfusion with peripheral blood progenitor cells (PBPCs) provides no improvement (Leyvraz et al 2008). Shortening the treatment by decreasing the interval between two cycles did not improve survival (Pujol et al 1997), nor did adding interferon as an adjuvant to chemotherapy (Van Zandwick et al 1997). Adding an antiangiogenic drug (thalidomide) improves survival at the expense of severe neurotoxicity, which precludes its use (Pujol et al 2007). Other antiangiogenics (marimastat) did not demonstrate any benefit. Maintenance therapy, which was usual until the 1980s, proved to have no effect on patient survival (Giaccone et al 1993) and nowadays 4 to 6 cycles are administered to patients. Even though a dose-response relationship was demonstrated decades ago (Cohen et al 1977), there has been no improvement beyond doses that can be safely administered without the need for PBPCs (Arriagada et al 1993).

Refractory and sensitive patients

About 95% of the patients with SCLC relapse after initial treatment, with overall survival expectation of only a few weeks. SCLC tumors develop a broad chemoresistance induced by the existence of drug-resistant clones at the beginning of the treatment (more frequent in ED) or the occurrence of these clones during treatment. This uncertainty explains why treatment of SCLC at relapse has been performed empirically rather than based on the knowledge of specific mechanisms of resistance involved (Huisman et al 1999).

Patients who relapse <3 months after first-line therapy are commonly called *refractory*, and patients who relapse at least 3 months after therapy are called *sensitive.* Refractory patients comprise those who never responded to induction therapy and progressed during this induction treatment together with those who responded but relapsed quickly within 3 months after the end of induction chemotherapy. When cisplatin and/or etoposide were not part of the initial treatment, high levels of response were published with this combination in relapsed patients, although in the early reports, duration of response rate to first line and duration of treatment-free interval after induction chemotherapy were not always detailed (Andersen et al 1990).

The usual practice is to reintroduce whenever possible, bearing in mind cumulative toxicity, the first-line therapy in those patients who relapse later, as the highest response rates were reported in this setting (Huisman et al 1999). However, one must be aware that the length of treatment-free interval before relapse depends on how frequent and exhaustive are disease assessments after the end of treatment. These data are never stated in published studies although they may have important effects on response rate. Moreover, in some studies, initial treatment was rechallenged if the treatment-free interval was ≥8 months (Postmus et al 1987) or even 2 years (Batist et al 1983). Although these studies are old, it is unlikely that the conclusions drawn would differ at this time, since there has been no modification in the induction treatment of this disease.

Studies devoted to second-line therapy in SCLC should be stratified on the refractory or sensitive character of the disease. Investigations of new agents with potentially no cross-resistance with induction therapy should be performed in refractory patients or sensitive patients who cannot be retreated with the same initial combination. Rechallenging the initial combination should be all the more considered as the treatment-free interval is ≥6 months (Eckardt 2003).

Topotecan in relapsed SCLC

This drug has been the most widely studied in the setting of relapsed SCLC. Topotecan, a semisynthetic, water-soluble analog of camptothecin, 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. Phase I studies resulted in a recommended dose and schedule of 1.5 mg/m²/day intravenously during 5 days every 3 weeks (Rowinsky et al 1992).

Phase II studies with topotecan as a single agent

Intravenous schedule

Only phase II studies published as full papers are discussed. Ardizzoni et al (1997) evaluated topotecan with this recommended schedule in 47 refractory and 45 sensitive patients with relapsed SCLC. Patients were less than 75 years old, PS 0–2, treated with one previous chemotherapy line. Previous rechallenge with the same chemotherapy regimen was allowed (7 patients). Brain metastases were not an exclusion criterion if asymptomatic. As a whole, there were 20 responses (21.7%, 95% CI 13.8%–31.6%), 3 in the refractory group (6.3%) and 17 (37.8%) in the sensitive group. There were 11 patients with brain metastases, and all who achieved a response outside the brain also responded at the brain level. Median duration of response was 7.6 months (95% CI 5.1–12.2 months). Median time to progression was 2.8 months (95% CI 2.2–3.9 months) and median overall survival was 5.4 months (95% CI 4.8–6.3 months) –6.9 months for sensitive patients and 4.7 months for refractory patients. Toxicity of topotecan was mainly hematological (75% of grade 3–4 neutropenia, 11.8% grade 3–4 anemia and 29.5% of grade 3–4 thrombopenia) and not cumulative. Non-hematological toxicity was mild.

Another phase II study was performed in 32 patients refractory to first-line cisplatin – etoposide therapy (Perez-Soler et al 1996). Three responses were observed (response rate 11%), of short duration for 2 (7 and 8 weeks). Median survival time was 20 weeks.

Topotecan given as salvage therapy in refractory patients pre-treated with irinotecan (+ cisplatin or carboplatine) did not appear effective, with 2 responses among 17 patients and a median survival time of 3.4 months (95% CI 1.7–5 months) (Park et al 2008).

A multicenter phase II study (Huber et al 2006) was performed in 170 patients in order to evaluate prospectively the efficacy and safety of topotecan with a starting dose of 1.25 mg/m² during 5 days and with dose adjustment according to toxicity. Patients with recurrent or refractory SCLC were stratified according to pre-treatment with a platinum-containing or platinum-free regimen and their response to pre-treatment. Patients were PS 0–2 and should have received only one previous line. In cases of no grade 3–4 toxicity after the first

cycle, dose could be augmented to 1.5 mg/m²/day. Further increase in doses was left to the investigator appreciation in case of the absence of grade 3–4 toxicity. Topotecan dose was reduced by 0.25 mg/m² in cases of grade 4 neutropenia lasting 7 days or longer, or complicated by fever or infection; platelet count of <25,000/µL, or neutrophil count of <1500 cells/µL[1] and platelet count <100,000/µL on day 22; and in cases of grade 3 or 4 non-hematological toxicity (except for nausea, vomiting and alopecia). In any case, the minimum topotecan dose had to be 1.0 mg/m²/day. No dose re-escalation was allowed. In case of complete response, 4 cycles were to be given. In cases of partial response or stable disease, treatment was given until progression or unacceptable toxicity.

A total of 76.8% of patients had performance status ECOG 0-1. The majority of patients (73.2%) had distant metastatic disease and 63.4% of patients had received a platinum-based primary therapy. The overall response rate to primary therapy was 76.8%. In total, 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. A total of 514 topotecan courses were received by 164 patients. Of these, 22.6% of patients (n = 37) received only 1 course of therapy, 52 patients (31.7%) received 2 courses, 6 patients received at least 3 courses, and 2.4% (n = 4) of patients received 8 courses. In 58.2% of courses (n = 299), the starting dose was maintained. The topotecan dose had to be reduced to 1.0 mg/m²/day in 8.9% (n = 46) of courses. The targeted dose of topotecan (1.5 mg/m²/day) 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/day to 98.2% of patients (n = 161). This starting dose was maintained in 46.5% of patients (n = 59) in course two. Dose was escalated to 1.5 mg/m²/day of topotecan in 37.8% of patients (n = 48), whereas in 15.7% (n = 20) it was reduced to 1.0 mg/m²/day. Median dose intensity of all administered cycles was 1.25 mg/m²/day.

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% of patients. No difference in response rates was seen between patients with or without platinum-containing pre-treatment. On the other hand, patients who had been refractory to primary therapy achieved a lower response rate (8.6% versus 17.1% in sensitive patients). Median duration of response was 13.6 (3.0–47.9) weeks and was not significantly different among the subgroups. Median time to progression for all patients was 8.0 weeks

(interquartile range 0.1–53.6 weeks). Median survival time was 23.4 weeks (interquartile range 0.9–92.4 weeks). Fifteen percent of patients were alive at 1 year.

Major side-effects were neutropenia and leukopenia, whereas anemia 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. The incidence thrombocytopenia was grade 3 and 4 in 10.3% and 5.0% of treatment courses (23.5% and 13.5% of patients), respectively. In total, 10% of patients received platelet transfusion (3.3% of treatment courses). Anemia grade 3 and 4 was less common (5.5% and 0.6% of all courses, respectively); in 3.6% of courses, red blood cell (RBC) transfusion was performed.

This study confirms that a reduced dose of topotecan 1.25 mg/m²/day is as effective as 1.5 mg/m²/day, with less hematological toxicity.

Oral topotecan

In a phase II randomized study iv topotecan with the classical schedule (1.5 mg/m²/day) was compared to oral topotecan (2.3 mg/m²/day, days 1–5, every 3 weeks) (von Pawel et al 2001), in a total of 106 sensitive patients (70% males). Fifty-two received oral topotecan and 54 received iv topotecan. Seventy percent had extensive disease and approximately 70% had also received prior radiotherapy. For both treatment regimens, the median number of courses was 4 (range: 1–12).

In this patient population, 12 patients (23%) receiving oral topotecan and 8 patients (15%) receiving iv topotecan responded to treatment. Among these, 3 (1 oral and 2 iv) had a complete response. The difference in response rates (oral vs iv) was 8.3% (95% CI, –6.6% to 23.1%), indicating that the true underlying response rate with the oral formulation is at worst 6.6% lower than that of the iv formulation, which is not a clinically meaningful difference. Sex ($p = 0.021$) and previous radiotherapy ($p = 0.015$) were statistically associated with increased probability of response. Female patients were 4.5 times more likely to respond than males and patients with no prior radiotherapy 4.9 times more likely to respond. Accounting simultaneously for all of the aforementioned prognostic factors in the logistic regression model, the oral topotecan patients were 1.6 times more likely to respond than the iv topotecan patients (95% CI for odds ratio: 0.50–5.15). In the multivariate model for response, patients were 30% more likely to respond than were those with less than 6 months time duration; however, this result was not statistically significant. The median survival was 32 weeks in the oral group and 25 weeks in the iv group. The multivariate analysis showed that absence of liver metastases and PS < 2 were both favorable independent prognostic factors.

There was also significant symptom improvement especially for chest pain, cough, dyspnea, anorexia, insomnia, hoarseness, fatigue, and interference with daily activity (from 16% to 42%). Again, the principal side effect was neutropenia, which occurred at a higher incidence in patients treated with iv topotecan. Myelosuppression was consistent with topotecan's profile, non cumulative and generally reversible. After use of oral topotecan, grade 4 neutropenia was observed in 35.3% of patients, whereas administration of iv topotecan resulted in grade 4 neutropenia, occurring in 67.3% of patients ($p = 0.001$); oral courses, 11.8%; iv courses, 32.5%. Two patients, 1 in each group, died of febrile neutropenia. The incidence of severe thrombocytopenia was similar with both treatment regimens: 27.5% of patients (8.0% of courses) in the oral topotecan group and 24.5% of patients (7.7% of courses) in the iv topotecan group. Platelet transfusions were given to 14.8% of patients treated with iv topotecan. The incidence of grade 3 or 4 anemia was also similar after either oral or iv topotecan: 31.4% of patients (10.4% of courses) in the oral topotecan group, and 30.2% of patients (10.5% of courses) in the iv topotecan group. RBC transfusions were given to 42.3% and 38.9% of patients in the respective groups.

Non-hematological toxicity consisted essentially of nausea and vomiting, mostly grade 1 and 2, but grade 3 nausea was observed in 11.5% of patients receiving oral topotecan and 3.7% of patients receiving iv topotecan. Grade 3 diarrhea was observed in 7.7% of the patients of oral group versus none of the iv group.

Weekly schedule

This schedule (topotecan 4 mg/m²/week) has been developed for ovarian cancer and was investigated in relapsed SCLC (Shah et al 2007). The rationale is based on preclinical studies and on the fact that topotecan, like taxanes and gemcitabine, which have demonstrated significant antitumor activity using weekly dosing schedule, is a S-phase specific drug. There was no response among 22 sensitive patients, and thus there is no indication to use this schedule at the present time.

Phase II studies with topotecan-based combinations

An EORTC phase II study of topotecan associated to cisplatin was performed in 110 patients among which 68 were sensitive (Ardizzoni et al 2003). Prior chemotherapy containing

cisplatin was permitted only in case of a partial response and completion of therapy at least 6 months ago. Cisplatin was given at the dose of 60 mg/m² on day 1 and topotecan at the dose of 0.75 mg/m² on days 1–5 every 3 weeks. A median number of 4 cycles were delivered to the sensitive patients and 3 to the refractory patients. Nineteen partial and 1 complete responses were obtained in the sensitive group (29%), whereas 10 partial responses occurred in the refractory group (23.8%). Median survival time was 6.4 months (95% CI 5.8–8 months) for the sensitive group and 6.1 months (95% CI 5.6–7.7 months) for the refractory group. Median time to progression was 4.7 months and 3 months, respectively. Grade 3–4 neutropenia was observed in approximately 75% of the patients and grade 3–4 thrombopenia in 74% of the sensitive patients and 64% of the refractory patients. Ten early deaths occurred, of which 7 could have been due to toxicity.

An other phase II study (Christodoulou et al 2006) evaluated the combination of cisplatin and topotecan with a different schedule: 20 mg/m² days 1–3 for cisplatin and 0.9 mg/m² days 1–3 for topotecan every 3 weeks. Thirty-four patients were included, 21 of whom were sensitive. The response rate was 18% (6 patients), with 2 complete responses and 3 partial responses in the sensitive group and only 1 partial response among the refractory group. Median survival time was 6.5 months for all patients (7.8 for sensitive and 6.2 for refractory patients). Median time to progression was 4.4. months for all patients (5.9 and 3.2 respectively for sensitive and refractory patients). Grade 3–4 neutropenia was observed in 42% of patients and grade 3–4 thrombocytopenia in 15%, less frequently than in the 5-day schedule.

Finally, topotecan and paclitaxel combination was investigated on a weekly schedule: paclitaxel 70 mg/m² and topotecan 1.75 mg/m² on days 1, 8, 15 repeated every 28 days in 45 sensitive patients (Stathopoulos et al 2006). Among these, 11 had already received paclitaxel as first-line therapy. There was 1 complete response and 10 partial responses. Median time to progression was 4 months and median survival time was 7 months (95% CI 4.2–9.8]. Grade 3–4 neutropenia was observed in 27% of the patients, grade 3 thrombocytopenia in 2.44%. The same combination has also been tested by the North Central Cancer Treatment Group with 84 patients accrued, but 78 eligible (Dy et al 2006). The treatment scheme was topotecan 1.0 mg/m² days 1–3 and paclitaxel 200 mg/m² day 3 every 4 weeks. After 6 patients (3 refractory and 3 sensitive) were included with good tolerance, the dose of topotecan was increased to 1.25 mg/m²/day. Refractory patients received a median of 3 cycles and sensitive patients

a median of 4 cycles. The overall objective response rate of patients with refractory disease was 8.7%; median time to progression was 2.8 months (95% CI 2.0–3.7) and accrual was closed after 23 patients due to insufficient clinical activity of this combination. The overall objective response rate of patients in sensitive relapse was 27.3%; median time to progression was 3.7 months (CI 2.2–5.3). Median survival time was 5.7 months in the refractory group (95% CI 4.8–7.5) and 6.9 months in the sensitive group (95% CI 5.8–8.4). The most frequently encountered grade 3 and 4 toxicities were neutropenia (92%), leukopenia (77%), thrombocytopenia (29%), fatigue (22%), and dyspnea (10%).

Phase III studies

In a randomized multicenter study, von Pawel et al (1999) compared cyclophosphamide, adriamycin, and vincristine (CAV) with topotecan as a single agent in patients who had relapse at least 60 days after completion of initial therapy. Patients received either topotecan as a 30 min/day infusion for 5 days every 21 days, or CAV infused on day 1 every 21 days. A total of 211 patients were enrolled. The response rates were 24.3% in patients treated with topotecan and 18.3% in patients treated with CAV (p = 0.285). Median times to progression were 13.3 weeks for the topotecan arm and 12.3 weeks for the CAV arm. Median survival times were 25 weeks for topotecan and 24.7 weeks for CAV. However, the size of the population of patients did not meet the criterion for a non inferiority study. The proportion of patients with symptom improvement (dyspnea, anorexia, hoarseness, fatigue, interference with daily activity) was greater in the topotecan arm than in the CAV group for 4 of the 8 symptoms evaluated. The authors concluded that topotecan was at least as effective as CAV in the treatment of patients with recurrent SCLC and resulted in improved symptom control. However, toxicity rates were high in both arms and alternative dose schedules of topotecan are currently favored.

Oral topotecan was compared to iv topotecan in a phase III study performed in 309 sensitive patients with relapsed SCLC (Eckardt et al 2007). Patients were assigned to treatment with either oral topotecan 2.3 mg/m²/day on days 1–5 or iv topotecan 1.5 mg/m²/day on days 1–5 every 21 days. Primary end point was response rate. In an intent-to-treat analysis, response rates were 18.3% (95% CI 12.2–24.4) with oral topotecan (n = 153) and 21.9% (95% CI 15.3–28.5) with iv topotecan (n = 151). Median survival time was 33.0 weeks for oral and 35.0 weeks for iv topotecan; 1- and 2-year survival rates were 32.6% and 12.4% for oral topotecan, respectively, and 29.2% and 7.1% for iv topotecan, respectively.

Grade 3–4 toxicity in patients who received oral and iv topotecan was: leukopenia in 65.7% and 75.3%, neutropenia in 73.2% and 87.8%, thrombocytopenia in 48.7% and 43.3%, grade 3 or 4 anemia in 23% and 31%, and sepsis in 3% and 3%, respectively. The most frequent non-hematologic adverse events (all grades) included nausea (43% oral; 42% iv), alopecia (26% oral; 30% iv), fatigue (31% oral; 36% iv), and diarrhea (36% oral; 20% iv).

Spiro et al 1989 demonstrated the favorable effect of chemotherapy on survival in relapsed SCLC in a randomized study comparing two durations of chemotherapy in first line then chemotherapy with methotrexate and doxorubicin to no treatment in second line. In a later, randomized study (O'Brien et al 2006), in patients with relapsed SCLC not considered as candidates for standard iv therapy, best supportive care (BSC) alone (n = 70) or oral topotecan (2.3 mg/m²/day, days 1–5, every 21 days) plus BSC (topotecan; n = 71) were compared. In an intent-to-treat analysis, survival was prolonged in the topotecan group (p = 0.0104). Median survival time was 13.9 weeks with BSC (95% CI 11.1–18.6 weeks), and 25.9 weeks with topotecan (95% CI 18.3–31.6 weeks). Partial responses were seen in 7% of patients receiving topotecan, with an additional 44% of patients achieving stable disease. Patients receiving topotecan had slower quality of life deterioration and greater symptom control. Principal toxicities with topotecan were hematologic: grade 4 neutropenia, 33%; grade 4 thrombocytopenia, 7%; and grade 3/4 anemia, 25%. Toxic deaths occurred in 4 patients (6%) in the topotecan arm. Early death rates (within 30 days after randomization) were 13% with BSC and 7% with topotecan.

Table 1 shows the results and Table 2 grade 3–4 toxicity observed with topotecan as a single agent in phase II and III studies.

Conclusion

Response rate to second-line therapy in SCLC patients is very low due to wide chemoresistance. However, response rate is highly dependent on the response to first-line therapy and on the duration of treatment-free interval. Topotecan, a topoisomerase I inhibitor, is an active drug in relapsed SCLC. It has at least partially no cross-resistance with other drugs commonly used in the treatment of SCLC except probably irinotecan. The response rate observed with topotecan is between 6% and 11.8% in refractory patients and between 15% and 37% in sensitive patients. Median survival time is between 3.6 and 5.4 months in refractory patients and 5 and 8 months in sensitive patients.

Patients with relapsed SCLC are often heavily pretreated and myelosuppression is the main toxicity expected. The usual 5-day schedule results in a quite important grade 3–4 hematological toxicity and is not very convenient for these patients with expected short-term survival. Oral topotecan appears to be as active and less toxic than iv topotecan, and is much more convenient. Weekly topotecan at this time does not appear as being active, and although more convenient than the 5-day iv schedule, it is not recommended. The combination of topotecan with either platinum salts or taxanes in the second-line setting is not superior to single-agent topotecan therapy. Thus, topotecan is indicated in refractory patients, taking into account the benefit/risk ratio in this poor

Table 1 Phase II/III studies of topotecan as single agent in relapsed SCLC

Schedule	Author	Year	Phase	No patients	RR %	RD (months)	TTP (months)	MST (months)
iv 1.5 mg/m² days 1–5	Ardizzoni	1997	II	45 s	37	4.75	4.06	6.9
				47 r	6	7.04	1.9	4.7
iv 1.5 mg/m² days 1–5	Perez-Soler	1998	II	32 r	11	–	–	4.6
iv 1.5 mg/m² days 1–5	Park	2008	II	17 r	11.8	–	1.7	3.4
iv adjusted to toxicity	Huber	2006	II	111 s	17.1	3.12	1.84	5.37
				59 r	8.6			
iv 1.5 mg/m² oral	Von Pawel	2001	R II	54 s	15	4.15	3.42	5.74
2.3 mg/m² days 1–5				52 s	23	3.19	3.00	7.34
Weekly 4 mg/m²	Shah	2007	II	22 s	0	–	1.37	5.00
iv 1.5 mg/m² days 1–5	Von Pawel	1999	III	211 ± s	24.3	3.3	3.05	5.74
oral 2.3 mg/m²	O'Brien	2006	III	71[a]	7	–	–	5.94
oral 2.3 mg/m²	Eckardt	2007	III	153	18.3	4.2	2.73	7.57
iv 1.5 mg/m² days 1–5				151	21.9	5.83	3.35	8.03

[a]unsuitable for iv chemotherapy.

Abbreviations: iv, intravenous; s, sensitive; r, refractory; R, randomized; RR, response rate; RD, response duration; TTP, time to progression; MST, median survival time.

Table 2 grade 3–4 hematological toxicities in phase II/III topotecan as single agent in relapsed SCLC (% patients)

Schedule	Author	Year	Phase	No patients	Grade 3–4 neutropenia	Grade 3–4 thrombocytopenia	Grade 3–4 anemia
iv 1.5 mg/m² days 1–5	Ardizzoni[a]	1997	II	45 s	74.9%	29.5%	11.8%
				47 r			
iv 1.5 mg/m² days 1–5	Perez-Soler[a]	1998	II	32 r	70%	31%	–
iv 1.5 mg/m² days 1–5	Park	2008	II	17 r	65%		
iv adjusted to toxicity	Huber	2006	II	111 s	27.6%	13.5%	1.7%
				59 r			
iv 1.5 mg/m² oral	Von Pawel	2001	R II	54 s	93.2%	49%	30.4%
2.3 mg/m² days 1–5				52 s	56.9%	52%	31.4%
Weekly 4 mg/m²	Shah	2007	II	22 s			
iv 1.5 mg/m² days 1–5	Von Pawel	1999	III	211 ± s	88.5%	57.6%	42.3%
oral 2.3 mg/m²	O'Brien	2006	III	71	61%	38%	25%
oral 2.3 mg/m²	Eckardt	2007	III	153	73.2 %	48.7%	22.6%
iv 1.5 mg/m² days 1–5				151	87.8%	43.3%	30.7%

[a]toxicity provided as a percentage of courses.

prognosis population and using the most convenient schedule (oral), and in sensitive patients when rechallenging the first-line treatment is not indicated.

Disclosures

The author has no conflicts of interest to disclose.

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