Beata Biernacka[1], Paweł Krawczyk[1], Jarosław Buczkowski[1], Anna Siwiec[1], Katarzyna Perżyło[1], Janusz Milanowski[1, 2]

[1]Department of Pneumonology, Allergy, and Oncology, Medical University in Lublin, Poland
Head: Prof. J. Milanowski, MD, PhD
[2]Institute of Rural Medicine in Lublin, Poland
Head: A. Horoch, MD, PhD

The value of topotecan in the second-line treatment of small-cell lung cancer. Preliminary report

Abstract

Introduction: Small-cell lung cancer (SCLC) is a highly aggressive malignancy with a high potential for growth and spread. Responses to first-line treatment are common but generally short-lived. Nearly all patients with extensive disease and most with limited disease relapse. The choice of second-line treatment depends on many factors, including previous treatment, previous response, time from completion of previous treatment to progression, and performance status. The most common chemotherapy regimen used in the second-line setting is the one which has led to long-term remission in the first-line setting. Topotecan monotherapy is increasingly used in second-line treatment, especially in patients with poor performance status.

Material and methods: Our aim was to evaluate the outcomes of topotecan monotherapy and to determine the effects of predictive/prognostic factors on the efficacy of the treatment. We investigated 42 patients with SCLC with extensive disease. Twenty-one subjects received topotecan monotherapy and the remaining ones received other chemotherapy regimens. Using the Cox proportional hazards model we demonstrated that such factors as the following reduce overall survival to the greatest degree: age over 65 years (HR = 2.35), anaemia (HR = 1.83), and poor performance status (HR = 1.51). A predictive/prognostic scale was created taking into account 6 factors that were assigned scores depending on the hazard ratio values.

Results: The survival probability of subjects managed with topotecan was non-significantly higher ($P = 0.097$) in the group of subjects who scored less than 10, compared to the group scoring 10 or more on our proposed scale. The scale failed to prove useful for predicting the course of SCLC in patients receiving other chemotherapy. Objective response to topotecan was observed in 5 patients (24%).

Conclusions: Precise qualification for topotecan monotherapy may prolong survival and increase the response rate.

Key words: small-cell lung cancer, second-line chemotherapy, overall survival, topotecan

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Introduction

Small-cell lung cancer (SCLC) is highly susceptible to chemotherapy, which is the principal mode of treatment in this tumour type. Chemotherapy in combination with radiotherapy is the standard of care in limited disease. In extensive disease, chemotherapy is used and only exceptionally radiotherapy in the palliative treatment of relapses. In patients with limited disease and complete response there is a high risk of central nervous system (CNS) metastases. Elective radiotherapy to the brain reduces the risk of CNS spread by a half. The role of elective radiotherapy in patients without complete response in the chest and with extensive disease remains unclear [1–3].

The following agents show considerable anticancer activity in first-line chemotherapy: cispla-

Addres for correspondence: Beata Biernacka, MNurs, Department of Pneumonology, Allergy, and Oncology, Medical University in Lublin, ul. Jaczewskiego 8, 20–950 Lublin, Poland, tel.: +48 81 724 4293, fax: +48 81 724 4823, e-mail: beatabiernacka1963@o2.pl

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tin, etoposide, cyclophosphamide, doxorubicin, and vincristine. The most commonly used regimens are the PE regimen (cisplatin plus etoposide), the CE regimen (carboplatin plus etoposide), or the CAV regimen (cyclophosphamide, doxorubicin plus vincristine). The selection of the PE regimen in the first-line setting is supported by the synergy of its components, relatively high activity, and good tolerability. Replacing cisplatin with carboplatin is not recommended unless clear contraindications to the former exist, such as renal failure. The less frequently used regimens include: CAE (cyclophosphamide, doxorubicin plus etoposide), V-ICE (carboplatin, iphosphamide, etoposide plus vincristine), and VIP-E (carboplatin, iphosphamide, cisplatin plus epirubicin).

Response to chemotherapy is observed in 80–90% of patients and is usually maintained for several months to more than a year. Median overall survival is 3 months in treatment-naïve patients with limited disease and 1.5 months in treatment-naïve patients with extensive disease. Correct treatment prolongs median survival to 14–20 months in patients with limited disease and to 9–11 months in patients with extensive disease [4–6].

First-line treatment means using chemotherapy in treatment-naïve patients whatever the stage of the disease. Second-line treatment may be considered in relapsed patients with good performance status who have responded to previous first-line chemotherapy and in patients refractory to first-line chemotherapy. In patients with a response of more than 3 months' duration from the completion of first-line treatment, the same agents as those in the first-line setting are used, while patients with early progression generally receive another combination chemotherapy or topotecan monotherapy [7].

Topotecan is a topoisomerase I inhibitor which relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex preventing religation of these single strand breaks and damages the DNA double-strand structure, leading to cytotoxic effects on proliferating cells, including tumour cells [8].

One of the novel cytostatic agents whose use in recurrent SCLC seems justified is the synthetic 9-aminoanthracycline amrubicin [9]. Certain hopes are pinned on enhancing the cytotoxic effects of amrubicin with the c-kit thyrosine kinase inhibitor imatinib. Amrubicin blocks topoisomerase I, while imatinib prevents phosphorylation of the Akt kinase, thereby blocking one of the principal signalling pathways in tumour cells whose activation is required for cell proliferation and establishing distant metastases. The efficacy of this chemotherapy has only been demonstrated in *in vivo* studies [8, 10].

The aim of our study was to evaluate the outcomes of second-line treatment with topotecan monotherapy versus other chemotherapy regimens in patients with SCLC managed at the Department of Pneumonology, Oncology, and Allergy, Medical University in Lublin, Poland, between 2005 and 2009. Another aim of the study was to define simple clinical predictive/prognostic factors that could help to qualify patients for topotecan treatment.

Material and methods

The study group comprised 42 patients with SCLC managed at the Department of Pneumonology, Oncology, and Allergy, Medical University in Lublin, Poland, between May 2005 and March 2009.

This was a retrospective study that concerned patients managed in real-life conditions. Qualification for topotecan treatment or other regimens was based on the outcome of the first-line treatment of these patients. If a patient had achieved long-term remission (of more than 3 months' duration) a platinum-based chemotherapy regimen was used. If the patient had achieved unsatisfactory response or had developed complications to platinum-based chemotherapy, topotecan was used in the second-line treatment.

In the group of patients who did not receive second-line topotecan, thirteen patients received platinum-based chemotherapy both in the first- and second-line settings. In six patients the PE or CE regimen was replaced by the CAV regimen, and two patients who had received first-line treatment with CAV received PE as their second-line treatment.

Twenty-one patients who progressed following prior chemotherapy received intravenous topotecan at the dose of 1.5 mg/m^2/day, while the other 21 patients received other chemotherapy regimens as their second-line treatment. All the patients had extensive disease when second-line chemotherapy was being initiated.

Before second-line topotecan and other chemotherapy regimens were initiated, imaging studies were performed (plain chest X-ray, chest CT, and in some cases brain MRI (or CT), whole-body bone scintigraphy, and abdominal ultrasound).

Before first-line chemotherapy all the patients in both study groups had their performance status assessed according to the ECOG/WHO/Zubrod score. The performance status assessment was repeated before the initiation of second-line treatment.

Table 1. Clinical characteristic of examined patients

	Topotekan	Other II-line chemotherapy
Gender	W = 5 M = 16	W = 3 M = 18
Age (years): mean ± standard deviation median	 61.6 ± 7.1 62	 62.1± 6.7 63
Number of patients	Topotekan = 21	PE = 6, KE = 3, CAV = 6, KN = 3, PN = 2, PN, then PE = 1
Disease stage at the I-line treatment beginning	LD = 6, ED = 15	LD = 9, ED = 12
Performance status at the start of first line treatment	PS0 = 10 PS1 = 6 PS2 = 5	PS0 = 8 PS1 = 10 PS2 = 3
Performance status at the start of second line treatment	PS1 = 6 PS2 = 15	PS0 = 5 PS1 = 6 PS2 = 10
Loss of body weight at the start of second line treatment	3–5% = 8 > 5% = 7	3–5% = 4 > 5% = 6
I-line chemotherapy scheme CAV = 1	PE = 18, PN = 1, KE = 1,	PE = 17, CAV = 2, PE , then KE = 1, CAV, then PE = 1
Number of cycles	6 cycles = 3, 5 cycles = 2, 4 cycles = 1, 3 cycles = 3, 2 cycles = 7, 1 cycle = 5	PE×6 = 2, PE×4 = 1, PE×3 = 1, PE×2 = 2, KE×4 = 3, KN×5 = 1, KN×2 = 1, KN×1 = 1, CAV×7 = 1, CAV×2 = 2, CAV×1 = 3, PN×2 = 1, PN×1 = 1, PN/PE×1 = 1
Time between I- and II-line treatment (months) mean ± standard deviation median	 3.95 ± 3.093 3	 4.79 ± 3.36 5

The topotecan-treated group included 6 patients with brain metastases, 8 with liver metastases, 2 with brain and liver metastases, and 2 with kidney metastases. The group receiving other chemotherapy regimens included 7 patients with liver metastases, 5 with brain metastases, 1 with liver and brain metastases, and 5 with kidney metastases. The remaining patients were classified as having extensive disease due to the local advancement of the tumour.

The demographic data, performance status, the first- and second-line regimens (patients with limited disease received radiotherapy in addition to chemotherapy), number of chemotherapy cycles, and the time from completion of first-line chemotherapy to commencement of the second-line chemotherapy are summarised in Table 1.

Based on laboratory parameters, we checked for the presence of anaemia (haemoglobin concentration and erythrocyte counts) and systemic inflammation (neutrophil absolute and relative counts, lymphocyte absolute and relative counts, leukocyte counts, C-reactive protein [CRP] concentration, and erythrocyte sedimentation rate [ESR]). We also documented neutropaenia in the first month of second-line treatment and thrombocytopaenia. We determined the presence and extent of weight loss within the six months preceding treatment (Table 1).

Using the Cox proportional hazards model we demonstrated that six factors reduced overall survival to the greatest extent. These factors were assigned scores depending on the hazard ratio (HR), survival reduction, and the *P* value. Due to the small number of patients investigated for establishing the predictive/prognostic scale, we also included factors whose effect on survival was non-significant (*P* values from 0.10 to 0.25) but whose HR values exceeded 1.5. Our analysis is therefore just an estimate and is largely arbitrary. A factor with *P* value below 0.05 was assigned 6 points and the remaining factors were assigned intermediate scores. We selected the following poor predictive/prognostic factors for chemotherapy:

— age above 65 years (2 points);

Table 2. Influence of chemotherapy on overall survival observation time in patients with recurrent SCLC

	Topotekan	Other II-line chemotherapy
Overall surival from diagnosis to death (months), number the death patients	12	17
mean ± standard deviation	13.35 ± 5.7	15.16 ± 8.77
median	12	12
Overall survival from II-line treatment beginning (months)	12	17
mean ± standard deviation	4.81 ± 4.1	4.67 ± 5.92
median	3.5	2
Follow up (months)		
mean ± standard deviation	8.22 ± 5.38	12.25 ± 12.31
median	7	8

— weight loss (3–5%: 2 points; >5%: 4 points);
— performance status (PS 0: 0 points; PS 1: 2 points; PS 2: 4 points);
— time from the completion of first-line chemotherapy to the commencement of second-line chemotherapy (6–12 months: 2 points; 3–6 months: 4 points; <3 months: 6 points);
— anaemia (degree of reduction in haemoglobin concentration below the lower limit of norm: 2 g/dl: 2 points; 4 g/dl: 4 points; 6 g/dl: 6 points);
— presence of inflammation (relative neutrophil count of 70% and WBC of 10–12 thousand/mm^3: 2 points; relative neutrophil count of 80%, WBC exceeding 15 thousand/mm^3, elevated CRP and ESR: 4 points).

We calculated overall survival (OS) from diagnosis to death, and from the commencement of second-line chemotherapy to death. We employed the Kaplan-Meier method to estimate the survival probability depending on the treatment used. We used the Cox model to calculate HR for survival for groups of patients differing in terms of demographic and clinical parameters. The statistical calculations were performed using Statistica 8.0 software.

Results

Response to first-line treatment was obtained in 16 patients (76%) receiving topotecan as the second-line treatment. Stabilisation of the disease was achieved in 3 patients (14%). Among the patients receiving other chemotherapy regimens in the second-line setting, 4 patients achieved stabilisation of the disease, while 10 patients (42.8%) achieved partial and 3 (14.28%) achieved complete response.

Topotecan treatment led to objective response in the form of partial remission in 5 patients (23.8%). Stabilisation of the disease was observed in 2 other patients. Objective response to topotecan was only observed in patients who had previously benefited from first-line treatment. Partial response to second-line treatment based on other regimens was only observed in 1 patient, and 4 patients achieved stabilisation of the disease.

Partial response and stabilisation of the disease following second-line topotecan were significantly more common than in the case of other regimens ($\chi^2 = 5.56$; $P < 0.05$), while median overall survival from the commencement of second-line treatment did not differ significantly between the study groups ($P = 0.59$) (Table 2). The survival probability in both groups was non-significantly lower in topotecan-treated patients compared to the other second-line chemotherapy regimens ($P = 0.87$) (Fig. 1). In patients with treatment response or stabilisation of the disease (surviving patients) median follow-up was 7 months in the topotecan-treated group and 8 months in the group receiving other chemotherapy regimens (Table 2).

We used the Cox proportional hazards model to analyse the effect of selected predictive/prognostic factors on the survival of patients receiving second-line chemotherapy. Having analysed the individual factors, we found that the following factors reduced overall survival to the greatest extent: age below 65 years (HR = 2.35; $P = 0.12$), anaemia (HR = 1.83; $P < 0.05$), and poor performance status (HR = 1.15; $P = 0.16$). Only anaemia significantly affected overall survival. In patients receiving other second-line chemotherapy regimens, the analysed factors did not affect overall survival from the initiation of treatment.

Based on the above analyses, we assigned the individual factors appropriate scores depending on the HR and P values, as described in the "Materials and methods" section above.

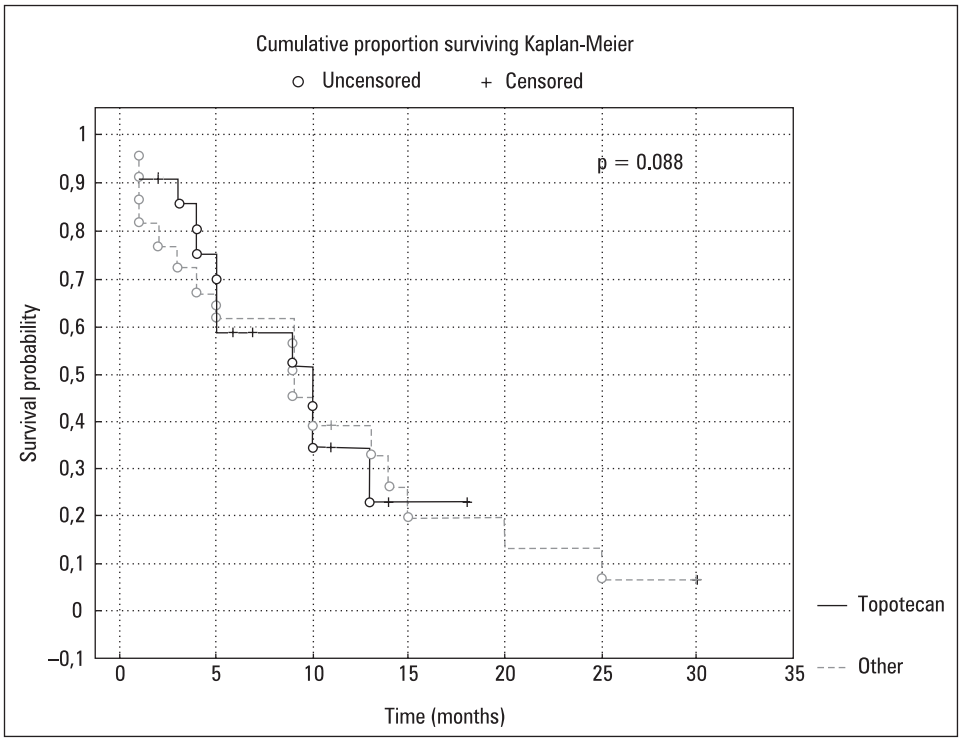

Figure 1. Cumulative proportion surviving of SCLC patients treated with topotecan or other second-line chemotherapy

We found that the multivariate analysis of the above factors using the Cox method was not useful in predicting overall survival when the entire group of patients was analysed ($\chi^2 = 3.39$; $P = 0.75$) and when the analysis was performed in the group of patients undergoing chemotherapy other than topotecan treatment ($\chi^2 = 3.77$; $P = 0.71$). In the group of patients receiving topotecan monotherapy the model affected overall survival in a non-significant manner ($\chi^2 = 11.09$; $P = 0.086$).

In the case of the entire group of patients ($\chi^2 = 0.029$; $P = 0.86$) and the patients receiving chemotherapy other than topotecan ($\chi^2 = 1.89$; $P = 0.17$), overall survival did not depend on our predictive/prognostic scores. The overall survival of topotecan-treated patients depended on the predictive/prognostic scoring non-significantly ($\chi^2 = 2.41$; $P = 0.12$) with higher scores adversely affecting the survival of patients managed with topotecan.

We investigated the distribution of scores among individual patients. The patients were divided in two groups: patients with scores below the fiftieth percentile and patients with scores from the fiftieth percentile up.

The survival probability of topotecan-treated patients was non-significantly higher (0.097) in the group of patients achieving 10 or more points on the proposed predictive/prognostic scale (Fig. 2). The effects of age (Fig. 3) and anaemia (Fig. 4) on the survival probability of patients receiving topotecan monotherapy were on the borderline of statistical significance. Such correlations were not found in patients receiving other chemotherapy regimens.

Discussion

Cytotoxic agents affect rapidly-dividing cells, which is why tumours with high proliferative index, such as SCLC, are more susceptible to them than slowly-proliferating ones. A considerable antitumour activity in SCLC is shown by alkylating agents (cisplatin, carboplatin, cyclophosphamide, iphosphamide), the mechanism of action of which involves interfering with the biological activity of DNA.

It is widely accepted that SCLC is considered a disseminated disease at the moment of diagnosis. One premise for using multidrug chemotherapy is the presence of tumour cells in different phases of the cell cycle showing various potential for proliferation. For this reason combination regimes result in 30-percent higher rates of objective response than monotherapy with platinum agents, iphosphamide, or etoposide [3, 11].

One exception to this rule is topotecan monotherapy in the second-line setting, which is being increasingly used in recurrent SCLC. The emergence of tumour cell clones that are resistant to chemotherapeutic agents used in first-line treatment

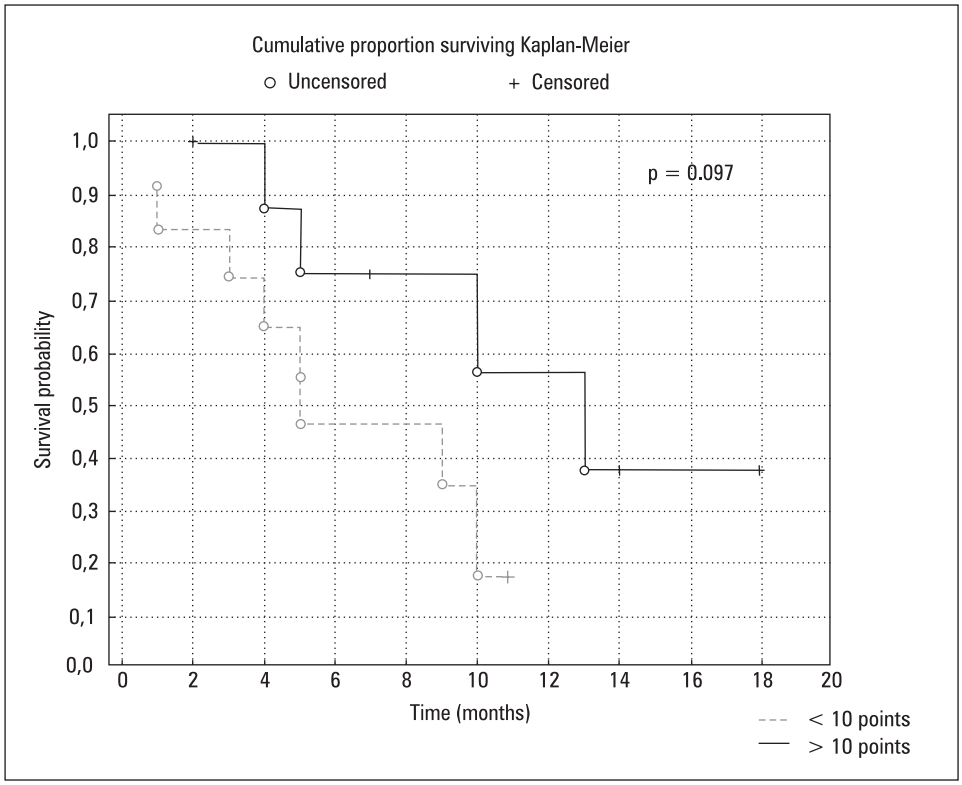

Figure 2. Cumulative proportion surviving of SCLC patients treated with topotecan depending on points by the scale of therapy predictive factors

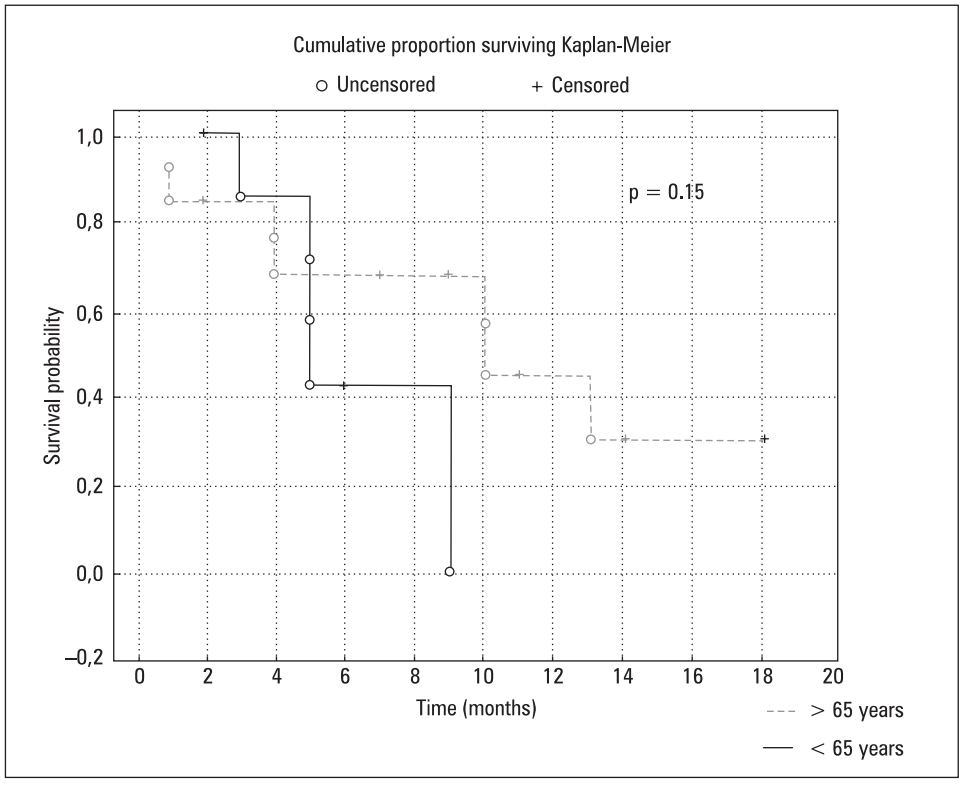

Figure 3. Cumulative proportion surviving of SCLC patients treated with topotecan depending on the patient's age

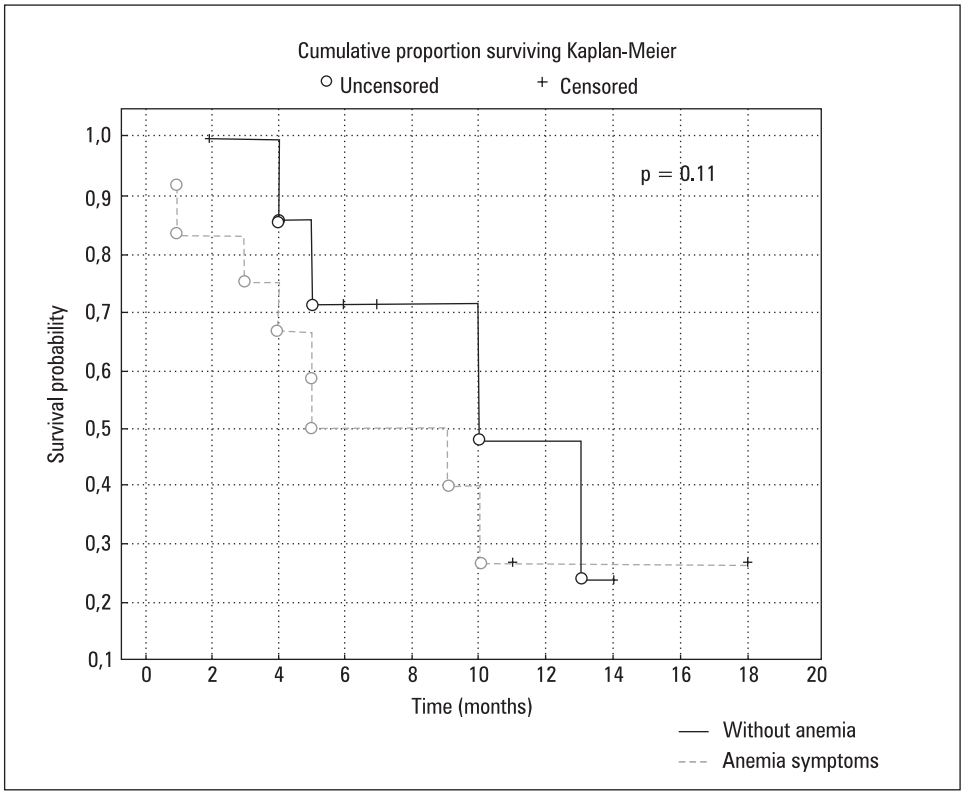

Figure 4. Cumulative proportion surviving of SCLC patients treated with Topotecan depending on anemia symptoms occurrence

warrants the use of agents with alternative mechanisms of action. Topotecan and irinotecan are synthetic and semisynthetic derivatives of camptothecin, and in contrast to the topoisomerase II inhibitors etoposide and teniposide, they inhibit topoisomerase I. Topotecan monotherapy is indicated as one of the most important second-line treatment options in patients who have failed on previous platinum-based combination chemotherapy [12].

The objective response rate in patients with recurrent SCLC receiving topotecan monotherapy ranges from 10% to as much as 40% - a considerable improvement in the quality of life and survival in patients receiving second-line treatment based on topotecan alone versus patients not receiving chemotherapy [13–15]. Furthermore, many studies suggest a lack of topotecan accumulation in healthy tissues and a lower severity of haematological toxicity (granulocytopenia rate of about 30%, thrombocytopenia rate of about 7%, anaemia rate of about 25%) following topotecan treatment compared to other cytostatic agents used in SCLC [16, 17]. The ability of topotecan to penetrate the blood-brain barrier is responsible for the cases of resolved CNS metastases reported in the literature [18]. The results obtained by various authors are, however, inconsistent, which is probably associated with the differences in the qualification criteria for topotecan treatment [16, 17].

A phase-III study by O'Brien et al. assessed the efficacy of oral topotecan at the dose of 2.3 mg/m^2/day versus placebo in patients with recurrent SCLC additionally receiving best supportive care (BSC). Complete response was achieved in 7% and stabilisation of the disease in 44% of topotecan-treated patients. Median overall survival was 6.5 months in topotecan-treated patients and 3.5 in patients receiving BSC alone. A short period from the completion of first-line treatment to the commencement of second-line treatment was a poor predictive factor for survival [19].

Subsequently, studies to compare the efficacy of topotecan versus other chemotherapy regimen in the second-line treatment of SCLC were performed. A study by Pawel et al. investigated patients receiving the CAV regimen (n = 104) or topotecan monotherapy (n = 107) for progression of the disease following platinum-based first-line chemotherapy. Response to topotecan was achieved in 24% of the patients and stabilisation in 20% of topotecan-treated patients. Slightly inferior responses were observed in CAV-treated patients: 18% and 20%, respectively. Median survival in both groups was identical and equalled 5.5 months [20].

Another phase III study, performed by Eckardt et al., compared the efficacy of oral (2.3 mg/m^2/day) versus intravenous (1.5 mg/m^2/day) topotecan in recurrent SCLC. A total of 309 patients were enrolled. Neither treatment proved superior. The response rate and median overall survival was 18.3% and 9 months, respectively, in the case or oral topotecan and 21.9% and 9.5 months, respectively, in the case of intravenous topotecan [21]. Of note is the fact that the effect of topotecan treatment in this study was better than that in the study by O'Brien et al. and median survival was better than that in the study by Von Pawel et al.

Ardizzoni et al. observed differences in the efficacy of topotecan in recurrent SCLC relative to the susceptibility to first-line chemotherapy. In susceptible patients achieving remission of more than 90 days' duration following first-line treatment, the objective response rate was 38% with complete responses accounting for as much as 13%. Median overall survival was about 7.5 months. The response rate in patients refractory to first-line cytostatic agents was only 6%, with median survival of a mere 5 months [16, 22]. Similar findings were obtained by O'Brien et al. These studies emphasise the significance of patient selection to study groups in topotecan efficacy analyses.

In our study the response rate in topotecan-treated patients was 24% and was high in comparison to the results obtained by other authors. It should be emphasised, however, that as many as 76% of the patients in this group had achieved objective response to first-line chemotherapy. This probably affected the relatively high rate of response to topotecan, but seemed not to affect the survival. The short duration of remission following first-line treatment was an important poor predictive factor in terms of survival in topotecan-treated patients. The time from the completion of first-line treatment to the commencement of topotecan monotherapy was included in the scoring system developed by us for the predictive/prognostic factors.

The median overall survival of patients receiving topotecan was only 3.5 months in our group, which was probably the result of the heterogenicity of the group, which was composed of patients with borderline performance status (PS 2/3), which still allowed them to be qualified for the treatment, and of patients with distant metastases, including several patients with metastases in two different organs. We did not observe any spectacular efficacy of topotecan in reducing the sizes of CNS metastases. The median follow-up of surviving patients who achieved remission or stabilisation of the disease following topotecan treatment was high (7 months). It was a group with good performance status and with long remissions following first-line treatment.

The use of topotecan in patients with poorer performance status (PS 2) and over the age of 65 years is supported by the study by Treat et al, who observed that the response rate to second-line topotecan monotherapy was 14% in patients with good performance status (n = 381) and even higher (17%) in patients with poorer performance status (PS 2; n = 98). However, elderly patients and patients with poorer performance status experienced more adverse reactions to chemotherapy (particularly anaemia and thrombocytopenia) and often required topotecan dose reduction. What is more, poor performance status was an adverse prognostic factor. The median survival was more than 9 months in patients with PS 0, 6.5 months in patients with PS 1, and only 4 months in patients with PS 2 [23].

This finding also explains the poor treatment outcomes we observed in our study. Although the response rate was high and resulted from the prior response to first-line chemotherapy, the reduction in median overall survival was largely associated with the poor performance status of patients qualified for topotecan treatment. Performance status assessment was one of the most important predictive/prognostic factors.

The classic favourable prognostic factors in lung cancer patients also include: lack of considerable weight loss, lack of anaemia and lack of immune response abnormalities (both granulocytopenia or agranulocytosis and the presence of inflammation), normal LDH activity, and age below 70 years [24]. In disseminated disease, further favourable prognostic factors include solitary metastasis and low local stage of the disease [25]. Most of these factors were taken into account when we were developing our predictive/prognostic model for topotecan-treated patients. We did not use the latter in our analysis as most patients had been diagnosed with distant metastases and the local stage of the disease was high.

Knowing the poor predictive/prognostic factors, we developed a summary scale that could be used in predicting the outcomes of second-line treatment of SCLC. As expected, it turned out that patients receiving topotecan and possessing the greatest number of adverse predictive/prognostic factors have poorer prognosis than patients without these factors. Our scale could not, however, be employed in patients receiving other second-line chemotherapy regimens, which was probably a result of the heterogenicity of the group, principal-

ly in terms of the differences in second-line therapy regimens and the number of completed chemotherapy cycles.

Our study confirmed the efficacy of topotecan in second-line treatment of recurrent SCLC. The use of multivariate analysis of predictive/prognostic factors may be useful for qualifying patients for topotecan treatment. It is a strong argument in favour of further studies of topotecan as it is currently an agent with the best-studied efficacy and tolerability in the treatment of recurrent SCLC [26].

Studies looking into using topotecan in patients with various stages of SCLC are ongoing. Eckardt et al. compared the efficacy of two treatment regimens: oral topotecan in combination with cisplatin (n = 389) versus the classic PE regimen (n = 395). In both treatment groups the objective response rate exceeded 60% and median survival exceeded 10 months. However, the rate of serious haematological complications was much higher in topotecan-treated patients than in patients receiving PE (59% vs. 84%) [27].

Recurrent lung cancer is also managed with dual chemotherapy based on topotecan plus cisplatin, paclitaxel, or vincristine. Response rates with this approach range from 19% to 21%, but median survival rarely exceeds 4 months. Given the numerous complications, this treatment of recurrent lung cancer is not superior to topotecan monotherapy [16].

Great hopes are being placed on the novel topoisomerase I inhibitor, amrubicin, used for the treatment of recurrent SCLC. Kair et al. demonstrated that amrubicin monotherapy led to an objective response rate of 44.8% in 66 patients and an increased median survival to 12 months. What is more, it was possible to achieve treatment response in the 35.3% of patients who had been refractory to first-line treatment cytostatic agents [28]. Inoue et al. compared the efficacy of topotecan and amrubicin in a group of 59 patients and showed that amrubicin led to treatment response in 17% of patients previously resistant to chemotherapy, while no objective response could be achieved with topotecan in this group [29]. Perhaps in the near future this agent will replace topotecan in second-line treatment of SCLC.

Conclusions

1. Objective response to topotecan treatment in recurrent SCLC is possible in more than 20% of patients. However, poor performance status, advanced stage, and the presence of other poor prognostic factors reduce median survival in topotecan-treated patients to less than 4 months.
2. As far as second-line treatment is concerned, it is possible to identify predictive/prognostic factors affecting survival following topotecan treatment. These factors are not as valuable as in other second-line regimens. It should, however, be noted that the analysed groups were very heterogenous and small. In view of the above, our predictive/prognostic model did not significantly affect the overall survival of topotecan-treated patients ($P = 0.086$). Nevertheless, a precise qualification for topotecan monotherapy may improve the survival and increase the response rate.

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