

# Management of Recurrent Small Cell Lung Cancer

Bryan J. Schneider, MD, Ann Arbor, Michigan

## Key Words

Small cell lung cancer, relapse, second-line chemotherapy, review, therapeutics

## Abstract

Small cell lung cancer remains one of the more frustrating malignancies for oncologists to treat. Although responses to initial platinum-based chemotherapy are high, most are not durable, and many patients are candidates for further palliative chemotherapy. Therapeutic options include reinduction or single-agent chemotherapy, depending on the duration of response to front-line treatment. Topotecan is the only approved agent for patients with relapsed disease. Several phase II studies have shown a modest benefit with other agents used today, although combination chemotherapy should be avoided because of increased toxicity. Palliative care should always be the focus, especially in patients with recurrent or chemorefractory small cell lung cancer and a poor performance status. (*JNCCN* 2008;6:323–331)

At initial diagnosis, 60% to 70% of patients with small cell lung cancer (SCLC) have clinically evident extensive-stage disease that is beyond the curative potential of combined modality therapy. Even among the remaining patients with limited-stage disease who can undergo concurrent chemotherapy plus radiation with curative intent, up to 80% will experience relapse, primarily at distant metastatic sites. These figures indicate that more than 90% of patients with SCLC will present with, or eventually develop, advanced disease—a setting in which systemic chemotherapy has become standard treatment

based on clinical trials showing benefits in survival and quality-of-life. In previously untreated patients with extensive-stage SCLC, platinum-based chemotherapy can realistically induce an objective tumor response in 60% to 80% of patients, with a median survival of 8 to 13 months. However, most patients, do not experience a durable response to initial chemotherapy and are subsequently eligible for further palliative systemic treatment.

This article discusses the current therapeutic options available for patients with advanced SCLC whose tumors relapsed after an initial response or who experienced resistance to initial chemotherapy. Historically, the median survival of patients with relapsed/resistant SCLC after first-line chemotherapy who did not receive further therapy was approximately 3 months.<sup>1</sup> However, the development of chemotherapy agents with novel mechanisms of action and relatively favorable toxicity profiles fueled an interest in studying chemotherapy in the relapsed/resistant setting (Table 1). Most of these studies are small phase II trials, and many have only been reported as meeting abstracts. To provide optimal information to guide current clinical care, this article focuses on fully published studies with agents that are either clinically available or in the advanced stages of clinical development.

A consistent theme among trials evaluating second-line therapy for SCLC is the comparison of outcome between patients with chemoresistant disease versus those with chemosensitive disease. Patients whose disease does not respond to front-line chemotherapy or who experience disease progression within 3 months of completing therapy are classified as having chemoresistant disease. Patients experiencing a durable response beyond 3 months are considered to have chemosensitive disease. Unsurprisingly, many of these trials show that patients with chemoresistant disease have worse outcomes, with a decreased chance of response to subsequent

From the University of Michigan, Ann Arbor, Michigan.

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Correspondence: Bryan J. Schneider, MD, University of Michigan, C340 MIB 5848, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5848. E-mail: bryansch@med.umich.edu

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chemotherapy and a shorter survival time compared with patients with chemosensitive SCLC.

## Reinduction Chemotherapy

Early trials evaluating second-line therapy for relapsed/resistant SCLC using non-cross-resistant

agents showed little benefit, prompting investigators to retry the first-line chemotherapy at relapse. Most of these trials were conducted in the 1980s with regimens not typically used today. One study evaluated 37 patients initially treated with cyclophosphamide, doxorubicin, and etoposide (CDE) who underwent reinduction with this regimen at relapse.<sup>2</sup> The median

**Table 1 Selected Clinical Trials Using Single-Agent Therapy for Relapsed/Resistant Small Cell Lung Cancer**

Agent	Dose and Schedule	N	Prior Platinum (%)	First-Line Chemotherapy Sensitivity	ORR (%)	MS (mo)	1-Year Survival (%)
Topotecan <sup>5</sup>	1.25 mg/m <sup>2</sup> days 1–5 q3wk	28	100	12 S 16 R	11.0	4.6	3.5
Topotecan <sup>6</sup>	1.5 mg/m <sup>2</sup> days 1–5 q3wk	93	42	46 S 47 R	37.8 6.4	6.9 4.7	30.0 10.0
Topotecan <sup>10</sup>	4 mg/m <sup>2</sup> weekly x 12 wk	103	NR	59 S 44 R	6.4 3.0	5.6 3.2	22.0 10.0
Topotecan <sup>11</sup>	4 mg/m <sup>2</sup> days 1, 8, 15 q4wk	22	100	22 S	0	5.0	NR
Irinotecan <sup>18</sup>	100 mg/m <sup>2</sup> q1wk	15	100	14 S 1 R	47.0	6.1	NR
Oral Etoposide <sup>27</sup>	50 mg/m <sup>2</sup> daily	26	96	NR	23.0	4.1	NR
Oral Etoposide <sup>28</sup>	50 mg/m <sup>2</sup> daily for 3 wk q4wk	22	68	20 S 2 R	45.5	3.5+	NR
Paclitaxel <sup>29</sup>	175 mg/m <sup>2</sup> q3wk	24	46	NR	29.0	3.3	NR
Docetaxel <sup>34</sup>	100 mg/m <sup>2</sup> q3wk	28	NR	NR	25.0	4.7*	NR
Gemcitabine <sup>36</sup>	1000 mg/m <sup>2</sup> days 1, 8, 15 q4wk	42	NR	24 S 18 R	16.7 5.6	7.3 6.9	NR
Gemcitabine <sup>37</sup>	1250 mg/m <sup>2</sup> days 1, 8 q3wk	27	100	15 S 12 R	0 0	8.8 4.2	NR
Vinorelbine <sup>42</sup>	25 mg/m <sup>2</sup> q1wk	24	100	17 S 7 R	12.5	4.7	NR
Ifosfamide <sup>44</sup>	5 g/m <sup>2</sup> 24-h infusion q3wk	14	0	14 R	43.0	10.9 <sup>†</sup>	NR
Pemetrexed <sup>45</sup>	500 mg/m <sup>2</sup> q3wk	43	NR	20 S 23 R	5.0 4.0	NR	NR
Pemetrexed <sup>46</sup>	500 mg/m <sup>2</sup> q3wk 900 mg/m <sup>2</sup> q3wk	38 78	NR	15 S 23 R 38 S 40 R	0 0 2.6 0	6.1 3.2 4.1 2.5	20.0 22.7 26.9 0
Amrubicin <sup>51</sup>	40 mg/m <sup>2</sup> days 1–3 q3wk	19	NR	7 S 12 R	37.0	NR	NR
Amrubicin <sup>52</sup>	40 mg/m <sup>2</sup> days 1–3 q3wk	60	100	44 S 16 R	52.0 50.0	11.6 10.3	45.5 40.3
Topotecan <sup>7</sup>	1.5 mg/m <sup>2</sup> days 1–5 q3wk	107	67	107 S	24.3	5.8	14.2
Cyclophosphamide <sup>7</sup>	1000 mg/m <sup>2</sup>						
Adriamycin	45 mg/m <sup>2</sup> q3wk	104	67	104 S	18.3	5.7	14.4
Vincristine	2 mg						

Abbreviations: MS, median survival; NR, not reported; ORR, objective response rate; R, chemoresistant; S, chemosensitive.  
\*Response duration.

<sup>†</sup>Median survival for the 6 patients that responded.

response duration to initial chemotherapy was approximately 8 months and overall response to reinduction was 62%. Patients had a much higher chance of experiencing response to reinduction if the previous response lasted longer than 8 months.

Similarly, another study reevaluated reinduction after initial treatment with CDE or the combination of cisplatin and etoposide and reported a response rate of 50% using the same regimen at relapse.<sup>3</sup> Median survival after reinduction therapy was 6 months, but most enrolled patients previously presented with limited-stage disease and the median treatment-free interval was almost 8 months, suggesting these patients had chemosensitive disease with a relatively long time to progression.

A third trial evaluated reinduction after initial treatment with various chemotherapy regimens, including carboplatin plus etoposide, and showed a response rate of 67% and a median survival of 5 months for the 10 patients who experienced response.<sup>4</sup> However, for the 5 patients who did not experience response, median survival was only 1 month. The authors concluded that the duration of response to initial therapy was the main predictor of response to reinduction chemotherapy, because most patients who experienced response had a time to progression exceeding 8 months. Based on these few trials, it has become accepted practice to consider reinduction chemotherapy if the duration of response to initial therapy exceeds 6 months.

## Topotecan

Topotecan is currently the only chemotherapeutic agent approved by the FDA for second-line treatment of SCLC and is a preferred option for patients ineligible for reinduction therapy. Phase II studies used doses of 1.25 to 1.5 mg/m<sup>2</sup> given intravenously on days 1 through 5 of a 21-day cycle, with response rates up to 38% and a median survival of approximately 5 months.<sup>5,6</sup> One trial of 47 patients with chemoresistant disease showed a response rate of only 6.4% compared with 37.8% among 46 patients with chemosensitive disease. Unsurprisingly, the median survival was also worse in the chemoresistant subgroup (4.7 vs. 6.9 months). Myelosuppression was the principal toxicity, with 75% of enrolled patients showing grade 3 or 4 neutropenia in this heavily pretreated population. Because of the lower response rates in patients with chemoresistant disease, topotecan is a less-favored

agent for patients who experience progression during first-line therapy or relapse within 3 months of treatment completion.

The phase III trial that led to the approval of this agent compared intravenous topotecan 1.5 mg/m<sup>2</sup> on days 1 through 5 of a 21-day cycle with a commonly used salvage regimen of CAV (cyclophosphamide 1000 mg/m<sup>2</sup>, doxorubicin 45 mg/m<sup>2</sup>, and vincristine 2 mg, given on day 1 of a 21-day cycle).<sup>7</sup> More than 200 patients were randomized and all had previously shown a response to platinum- or etoposide-based chemotherapy for at least 60 days. The response rate (24.3% vs. 18.3%), median survival (25 vs. 24.7 weeks), and 1-year survival (14.2% vs. 14.4%) were nearly identical between the arms. Control of disease symptoms seemed to favor the use of topotecan, with patients experiencing decreased dyspnea, anorexia, and fatigue compared with those treated with CAV. Side effects were comparable, with less grade 3 or 4 neutropenia, but more grade 4 thrombocytopenia and grade 3 or 4 anemia in the topotecan arm.

Retrospective analyses of trials using this dose and schedule of topotecan suggest that elderly patients ( $\geq 65$  years) and patients with a Zubrod performance status (PS) of 2 experience a similar degree of benefit compared with younger or more functional patients who have comparable tumor response rates, symptom management, and hematologic side effects.<sup>8,9</sup> Unsurprisingly, patients with a PS of 2 showed a shorter median survival than those with a PS of 0 (3.7 vs. 8.3 months;  $P < .001$ ), despite similar degree of symptom control and neutropenia.

The approved dose and schedule for topotecan has been associated with significant toxicity (mostly related to myelosuppression) and a modest clinical benefit. Therefore, newer approaches are being investigated, including alternate dosing schedules, use of the oral formulation, and combinations with other cytotoxic agents. Recently, a large phase II study suggested that weekly administration of intravenous topotecan 4 mg/m<sup>2</sup> for 12 weeks may be as effective as the traditional 5-day infusion schedule, with a similar median survival of approximately 5 months but less toxicity.<sup>10</sup> In this study, 59 patients with chemosensitive disease and 44 with chemorefractory disease showed a response rate, median survival, and 1-year survival of 6.4% vs. 3.0%, 5.6 vs. 3.2 months, and 22% vs. 10%, respectively. Grade 3 or 4 neutropenia was only seen in 17% of patients and thrombocytopenia in 21%, suggesting a

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more favorable toxicity profile with weekly administration, although this has not been confirmed in a prospective phase III trial. Conflicting results were obtained from a similar study evaluating topotecan 4 mg/m<sup>2</sup> weekly for 3 weeks followed by a 1-week break in 22 patients.<sup>11</sup> Although no responses were seen, 18% of patients showed disease stability and the median survival was 5 months, which is comparable with results of other phase II studies. None of the patients showed grade 3 or 4 neutropenia and the authors concluded that this regimen is well tolerated and may offer clinical benefit despite lack of disease response.

The oral formulation of topotecan has been compared with the standard intravenous regimen in the relapsed/resistant setting, showing comparable response rates and median survival but reduced neutropenia.<sup>12,13</sup> In addition, a large phase III trial showed greater symptom control and a survival benefit using oral topotecan compared with best supportive care, with a median survival of 6.0 months versus 3.2 months ( $P = .01$ ).<sup>1</sup> This trial is the first to clearly show a survival advantage for chemotherapy versus no chemotherapy in the relapsed/resistant setting. However, oral topotecan is currently not commercially available in the United States.

Finally, several phase II studies have used topotecan in combination with other agents, including paclitaxel, cisplatin, etoposide, or gemcitabine, for relapsed SCLC.<sup>14-17</sup> These topotecan-based doublets have failed to show a substantial improvement in response rates or survival, and toxicity was typically increased compared with topotecan monotherapy. These combinations are therefore not recommended outside of a clinical trial.

### Other Topoisomerase Inhibitors

Irinotecan, a topoisomerase I inhibitor, has been investigated in relapsed/resistant SCLC almost exclusively in the Japanese patient population. As monotherapy, irinotecan 100 mg/m<sup>2</sup> given weekly showed a response rate of approximately 50% and a median survival of 6.1 months in patients who had undergone prior platinum- or etoposide-based chemotherapy.<sup>18,19</sup> Dose-limiting side effects included leukopenia, nausea, vomiting, and diarrhea. In 2 phase II trials, the combination of irinotecan 60 mg/m<sup>2</sup> plus cisplatin 30 mg/m<sup>2</sup> given on days 1, 8, and 15 of a 28-day cycle has shown response rates of 30% and 80% and a median survival

of approximately 8 months.<sup>20,21</sup> The substitution of cisplatin with carboplatin produced similar results in 2 small phase II trials.<sup>22,23</sup> In a mostly chemosensitive population, an aggressive schedule of irinotecan 70 mg/m<sup>2</sup> administered on days 1, 8, and 15 plus etoposide 80 mg/m<sup>2</sup> on days 1 through 3 of a 28-day cycle showed a response rate of 71% and median and 1-year survivals of 8.9 months and 28%, respectively.<sup>24</sup> Despite growth factor support, almost 60% of patients showed grade 3 or 4 neutropenia.

Finally, 2 phase II trials of irinotecan and cisplatin with either etoposide or ifosfamide showed response rates of 78% and 94%, respectively, and a median survival of almost 1 year in a predominantly chemosensitive population with relapsed SCLC.<sup>25,26</sup> The trial using ifosfamide required a dose reduction in both cisplatin and irinotecan midstudy because of intolerable hematologic toxicity that included grade 3/4 neutropenia and thrombocytopenia in 83% and 50% of the patients, respectively. Given that the response and survival data for irinotecan-treated patients in Japan are consistently better than results of similar western trials, and the fact that none of the patients in the above-mentioned studies received prior topotecan, these results are difficult to apply to the U.S. patient population. Irinotecan monotherapy is a reasonable therapeutic option for patients who have not previously received topotecan.

Oral etoposide, an inhibitor of topoisomerase II, has shown effectiveness after intravenous etoposide use and is a well-tolerated agent in patients with a marginal PS. A regimen of oral etoposide 50 mg/m<sup>2</sup> administered daily was evaluated in a small phase II trial of patients with relapsed/resistant SCLC, most of whom had received prior intravenous etoposide plus cisplatin and CAV.<sup>27</sup> The response rate in this heavily pretreated population was 23%, with a median survival of 4.1 months. Hematologic toxicity was the predominant side effect, with 50% grade 3/4 leukopenia, and patients were recommended to undergo 3 weeks of therapy followed by a 1-week break. In a subsequent trial, 22 patients initially treated with CAV or etoposide-based chemotherapy received oral etoposide 50 mg/m<sup>2</sup> daily for 21 days of a 28-day cycle and showed a response rate of 45.5% and a median survival of 3.5 months.<sup>28</sup> Previous intravenous etoposide did not affect the response rate to the oral regimen; however, no patient showed response who did not experience response to front-line chemotherapy.

## Taxanes

Both paclitaxel and docetaxel have been evaluated in small phase II studies for the treatment of relapsed/resistant SCLC. Paclitaxel monotherapy at a dose of 175 mg/m<sup>2</sup> was administered every 21 days in a heavily pretreated population in which most subjects had undergone 2 or more prior chemotherapy regimens.<sup>29</sup> The response rate was 29%, with a median survival of 3.3 months, and the predominant side effects included leukopenia and peripheral neuropathy. Because of the impressive response rate after extensive prior therapy and the tolerable toxicity profile, paclitaxel monotherapy has become one of the preferred agents for chemoresistant SCLC.

When doxorubicin 40 mg/m<sup>2</sup> was combined with paclitaxel, a response rate of 41% and median survival of 5.7 months were reported.<sup>30</sup> Two partial responses were seen among the 14 patients with chemoresistant disease, and it was suggested that this might be an effective combination in this patient population. However, paclitaxel in combination with gemcitabine showed no responses in a heavily pretreated population and was deemed inactive as salvage treatment.<sup>31</sup> In contrast, paclitaxel in combination with carboplatin showed a remarkable response rate of 74% and median survival of 7.1 months in patients who experienced relapse within 3 months after first-line treatment with CDE.<sup>32</sup> Because most patients are initially treated with platinum-based regimens, these results are difficult to apply to modern practice.

Finally, a recent trial reported in abstract form evaluated paclitaxel 75 mg/m<sup>2</sup> plus irinotecan 50 mg/m<sup>2</sup>, with both drugs administered on days 1 and 8 of a 21-day cycle to 32 patients who experienced relapse after 1 prior chemotherapy regimen.<sup>33</sup> The response rate was 37%, median survival was 4.5 months, and the 1-year survival rate was 15%. Side effects included neutropenia and fatigue. The number of patients with chemoresistant SCLC enrolled was not discussed and a full report on the 55 total patients enrolled is awaited.

Docetaxel has also shown a modest response in this patient population. Two small phase II trials evaluated 60 and 100 mg/m<sup>2</sup> of docetaxel administered every 21 days with response rates of 13% and 25%, respectively.<sup>34,35</sup> No survival data were reported and the major side effects included neutropenia, asthenia, and skin toxicity.

## Gemcitabine

Gemcitabine has been evaluated in several large phase II studies as monotherapy and in combination with irinotecan for the treatment of relapsed/resistant SCLC. As monotherapy, standard doses of 1000 to 1250 mg/m<sup>2</sup> showed response rates of 0% and 17%, with median survivals of 4.2 to 8.8 months, and hematologic toxicity was the predominant side effect.<sup>36,37</sup> Almost half of the patients in each trial were deemed to have chemoresistant disease and only 1 patient showed a partial response in this subpopulation. Although gemcitabine monotherapy has a favorable toxicity profile, the clinical benefit based on these 2 trials seems modest at best.

Gemcitabine, 1000 mg/m<sup>2</sup>, combined with irinotecan, 100 mg/m<sup>2</sup>, given on days 1 and 8 of a 21-day cycle showed response rates of 17% to 21% and a median survival up to 7.1 months for patients with chemosensitive disease.<sup>38,39</sup> Side effects were mostly hematologic, with nausea, vomiting, and diarrhea the predominant nonhematologic toxicities. For the patients with chemorefractory disease, the response rate was 11% and median survival was 3.5 months, again suggesting this combination is not superior to single-agent therapy. Similarly, 2 studies evaluated gemcitabine plus vinorelbine with response rates of 6% to 10%, median survivals of 4.5 to 5 months, and a high rate of neutropenic fever.<sup>40,41</sup> The response rate in patients with chemorefractory disease was negligible and this combination was deemed ineffective as salvage therapy.

## Vinorelbine

Vinorelbine has been evaluated as monotherapy at doses of 25 to 30 mg/m<sup>2</sup> given weekly in mostly patients with chemosensitive disease with response rates of 12% to 16% and hematologic toxicity as the predominant side effect.<sup>42,43</sup> One trial showed a median survival of 4.7 months for the 24 patients enrolled, 16 of whom underwent 2 or more previous chemotherapy regimens. These 2 small phase II studies showed a modest response rate and acceptable toxicity for patients with relapsed SCLC; however, the paucity of data with vinorelbine has limited enthusiasm for its use as second- or third-line therapy.

## Ifosfamide

Data on the use of ifosfamide as monotherapy for relapsed/resistant SCLC are limited to a few, small

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phase II studies mostly conducted in the early 1980s. One study of note used the front-line combination of etoposide, doxorubicin, and vincristine (VPAV) followed by 2 to 3 courses of consolidation ifosfamide  $5 \text{ g/m}^2$  intravenously over 24-hours with infusional mesna over 32-hours.<sup>44</sup> Importantly, patients showing no response after 2 cycles of VPAV crossed over to receive ifosfamide. Among these 14 patients with chemorefractory disease, 6 (43%) showed a partial response, suggesting that ifosfamide monotherapy may be a reasonable option for the treatment of chemorefractory SCLC. In the palliative setting, however, response must be weighed against the inconvenience of a prolonged infusion in addition to the potential side effects that include neutropenia, esophagitis, hemorrhagic cystitis, nausea, and neurotoxicity.

### Pemetrexed

Recently, 2 abstracts were presented at the ASCO annual conference, both of which reported disappointing results with the use of pemetrexed monotherapy in the treatment of relapsed/resistant SCLC. One trial enrolled 43 patients (20 with chemosensitive and 23 with chemorefractory disease) who received the standard dose of pemetrexed,  $500 \text{ mg/m}^2$ , every 21 days, with only 1 partial response seen in each subgroup.<sup>45</sup> Another trial treated 56 chemosensitive and 65 chemorefractory patients with  $500 \text{ mg/m}^2$  or  $900 \text{ mg/m}^2$  of pemetrexed every 21 days, and a partial response was only experienced by 1 patient who had chemosensitive disease.<sup>46</sup> The higher dose of pemetrexed was not more effective. The early results of these 2 studies indicate a minimal benefit of this agent in the setting of relapsed/resistant SCLC.

### Multi-Drug Combinations

Multi-drug combinations for the treatment of relapsed/resistant SCLC have not shown consistent improvements in survival and are always associated with substantial increases in toxicity compared with single-agent therapies. For example, the triplet combination of paclitaxel,  $175 \text{ mg/m}^2$ ; ifosfamide,  $5 \text{ g/m}^2$ ; and cisplatin,  $100 \text{ mg/m}^2$ , was evaluated in patients with good PS who experienced progression after initial therapy with carboplatin and etoposide.<sup>47</sup> Although the response rate was 73% (70% in patients with chemoresistant disease), the median survival was only

6.4 months and toxicity included 73% grade 3/4 neutropenia plus 18% febrile neutropenia despite mandatory growth factor support. Similarly, a regimen of daily oral etoposide,  $37.5 \text{ mg/m}^2$ ; ifosfamide,  $1.2 \text{ g/m}^2$ , on days 1 through 4; plus cisplatin,  $20 \text{ mg/m}^2$ , on days 1 through 4 of a 21-day cycle was studied in 42 patients, most of whom had undergone initial treatment with cisplatin and etoposide.<sup>48</sup> The response rate and median survival were 55% and 6.7 months, respectively, but 31% were hospitalized for neutropenic fever and 10% died of neutropenic sepsis despite reducing etoposide to a 14-day treatment. Finally, CAV has shown a fairly low response rate after initial platinum and etoposide. A small phase II study of CAV that included 29 patients previously treated with platinum-based chemotherapy showed a response rate of 28% and a median survival of only 3.5 months.<sup>49</sup> A large phase III trial evaluating various schedules of CAV administered before, after, or alternating with cisplatin plus etoposide included 41 patients initially treated with cisplatin and etoposide followed by CAV at relapse.<sup>50</sup> The response rate was 14% for patients with chemosensitive disease and 8% for those with chemoresistant disease, with a median survival of 4.3 months for the entire cohort. The rates of myelosuppression and gastrointestinal toxicity mirrored what is seen with cisplatin and etoposide therapy. With modest clinical benefit, CAV is no longer a favored regimen in the palliative setting and is not recommended for patients with chemoresistant disease.

### Future Therapy

Over the past few years, several new agents have been evaluated in small phase I and II clinical trials in patients with relapsed SCLC. Thus far, the number of objective responses observed remains modest, but a few agents seem to show promising effectiveness and tolerability. Amrubicin, a fully synthetic anthracycline that inhibits DNA topoisomerase II, is one of the most promising agents. Two phase II studies of amrubicin,  $40 \text{ mg/m}^2$ , given intravenously on days 1 through 3 of a 21-day cycle in patients with recurrent SCLC showed response rates of 37% to 52% and median survival up to 11.2 months.<sup>51,52</sup> Interestingly, 1 study showed a response rate of 50% in 16 patients deemed to have chemoresistant disease. Myelosuppression was the major toxicity with 70% grade 3 or 4 leukopenia. Trials are ongoing to further evaluate amrubicin, including a randomized

phase II trial and a planned phase III trial with topotecan as the control.<sup>53</sup>

Picoplatin is a platinum analog designed to overcome platinum resistance. A preliminary report from a phase II study indicates potential clinical benefit with a median survival of 6.5 months in patients with chemorefractory disease when given as monotherapy in the second-line setting.<sup>54</sup> A phase III study is currently underway. The alkylating agent VNP40101M has shown response rates of 29% and 5% in patients with chemosensitive disease and chemoresistant disease, respectively.<sup>55</sup> Interestingly, 3 of 16 patients with brain metastases showed a response in the central nervous system, suggesting potential benefit for patients with central nervous system recurrence.

Although numerous molecularly targeted agents are currently being evaluated in an attempt to overcome the molecular heterogeneity and resistance inherent in SCLC, none of these agents has been found to alter the clinical history of this disease. Inhibition of neoangiogenesis seems to be the most promising given the consistent overexpression of vascular endothelial growth factor in SCLC and its association with a poor prognosis.<sup>56</sup> The hope is that newer targeted treatment approaches will favorably impact prognosis and quality-of-life of all patients with cancer, including those with recurrent SCLC, which is a condition that desperately needs these advances.

## Management Guidelines

Treatment of advanced SCLC after failure of initial chemotherapy remains a challenge. Clearly, the major goal of any intervention in this setting must be to improve quality-of-life, because advanced SCLC remains a terminal disease. Providing optimal palliative care, with or without further anticancer therapy, must be the primary goal of the managing oncology team. Most patients, especially those with poor or marginal PS, may not benefit from further chemotherapy, and early initiation of hospice services must be presented to these patients and their families as a viable option that may offer the best potential to optimize their quality-of-life. This is illustrated in a retrospective study that evaluated clinical prognostic factors in 229 patients with SCLC who received second-line therapy and found that PS was the only significant predictor of survival in both patients with chemosensitive and chemoresistant disease.<sup>57</sup>

Nearly all trials evaluating the usefulness of chemotherapy in patients with relapsed/resistant SCLC are relatively small, uncontrolled phase II trials with varying eligibility criteria and an uneven distribution of patients with chemosensitive and chemoresistant disease. Only topotecan has been evaluated in a few controlled phase III trials. Aside from these trials, the nature of the available literature confounds comparisons among treatment options and limits the translation of trial results into broadly applicable evidence-based practice guidelines. Several important concepts must be considered when attempting to apply the results of clinical trials to the care of patients with relapsed/resistant SCLC. Because of eligibility criteria requiring good PS, normal or near normal organ function, and limited comorbidity, all trials of therapy for patients with relapsed/resistant SCLC involve an implicit selection bias. Many patients are deemed unfit for second-line studies, and those enrolled on clinical trials represent “the best of the best,” with most having PS 0 to 1. Therefore, it is not surprising that the survival results from many trials of second-line chemotherapy, especially those using multidrug combinations, seem to approach those from trials of first-line therapy. Outside of the randomized controlled trial setting, the question of whether these relatively favorable results are caused by the treatment or the selection of patients with indolent, nondebilitating disease remains unanswered.

Many patients with relapsed/resistant SCLC do not fit into the good PS category because of constitutional symptoms related to advanced cancer and the residual effects of toxicity from prior treatment. For patients with PS 3, the risks of therapy seem to outweigh any potential benefits. However, many patients are unwilling to accept best supportive care and wish to proceed with further therapy. The oncologist is responsible for presenting an honest overview of the potential benefits and risks of available treatment options, including investigational clinical trials and best supportive care, along with a clear indication that the disease is terminal and that all treatment, including chemotherapy, is given with palliative intent. When the decision has been made to proceed with further therapy, the choice of specific treatment must be determined on an individual basis, taking into account factors such as PS, previous treatment regimens, response to prior therapy, treatment-free interval, residual side

effects from prior therapy, and underlying comorbid conditions.

For patients with relapsed/resistant SCLC who have maintained a good PS, further treatment remains an option. Reinduction therapy could be considered for patients experiencing a progression-free interval beyond 6 months. Topotecan is the only FDA-approved agent for second-line treatment of relapsed/resistant SCLC. Phase II data suggest that other agents, such as paclitaxel, docetaxel, oral etoposide, vinorelbine, and gemcitabine, have similarly modest activity in patients with relapsed/resistant SCLC, although these agents have not been directly compared with topotecan in randomized trials. Single-agent therapy remains the standard therapeutic option. Combination chemotherapy regimens cannot be recommended because of lack of evidence of a survival benefit and their increased toxicity. Because of the modest benefits reported with standard therapy, enrollment on clinical trials, including phase I trials, clearly remains a reasonable and necessary option for all patients with good PS and relapsed/resistant SCLC.

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