Salvador Dali (Spanish, 1904-89). *Daddy Longlegs of the Evening - Hope!* (1940). Oil on canvas, 10 x 20 inches. Collection of the Salvador Dali Museum, St. Petersburg, Florida. Copyright 1997, Salvador Dali Museum, Inc.

New Agents in the Management of Non-Small-Cell Lung Cancer

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A relatively low toxicity profile of many new drugs should result in overall net benefit for patients with advanced lung cancer.

Background: *Non-small-cell carcinoma of the lung has long been considered a chemotherapeutically resistant neoplasm. Newer agents and combinations are being tested.*
Methods: *The authors have reviewed data on recent and active phase I and phase II trials of several new agents and combinations.*
Results: *New drugs that affect both response rates and survival include vinorelbine, paclitaxel, docetaxel, gemcitabine, topotecan, and irinotecan.*
Conclusions: *The advent of several relatively well-tolerated agents that alone have beneficial effects in advanced non-small-cell lung cancer provides reasonable hope that more effective drug combinations will soon be available for this disease.*

Introduction

Although real progress has been made in the management of advanced non-small-cell lung cancer (NSCLC) in recent years, this malignancy continues to be viewed as an illness for which little can be done other than surgery. Consequently, NSCLC is frequently treated suboptimally.[1-3] There are many possible explanations for this situation but, undoubtedly, the attitude of primary care physicians regarding the "value" of existing therapies is paramount.[2,4,5] Studies indicate that non-oncologists (and many oncologists) often believe that treatment of lung cancer provides little or no survival benefit to their patients.[5,6] In addition, treatment of lung cancer is commonly perceived as costly and even harmful to the patient. Although prevalent, these attitudes are not supported by the available published data.[7] For example, a recently published meta-analysis of chemotherapy improves survival data in patients with advanced NSCLC compared to best supportive care.[8] Although the survival impact of existing chemotherapy regimens is relatively modest, it is comparable to that achieved with chemotherapy in many other solid tumors.

Those opposed to the use of chemotherapy in the treatment of advanced NSCLC commonly argue that it is not cost effective and that the modest survival benefit achieved with chemotherapy is outweighed by the toxicities engendered. However, a number of recent studies have shown that tumor-related symptoms frequently improve with the use of chemotherapy, in many instances to a degree unanticipated relative to the level of objective tumor response.[9,10] The economic aspects of lung cancer therapy have been addressed in several studies, including an analysis performed by the National Cancer Institute of Canada.[11,12] In this study, chemotherapy was found to be more cost effective than supportive care primarily because patients receiving chemotherapy required fewer hospitalizations and less radiotherapy. Thus, the available data indicate that a strong argument can be made for administering chemotherapy to good performance status NSCLC patients as it is both cost effective and useful for the palliation of symptoms.

While existing chemotherapy agents provide some measure of benefit in the management of NSCLC, more effective therapies are needed. Rather than focusing on older drugs and regimens, this article focuses on newer agents with promising activity against NSCLC including vinorelbine, paclitaxel, docetaxel, gemcitabine, topotecan, and irinotecan. These newer drugs, both individually and in combination with other active agents, hold promise for further improvement in the management of NSCLC.

Vinorelbine

Vinorelbine (Navelbine) is a new semisynthetic vinca alkaloid with a mechanism of action similar to that of its congeners. However, in preclinical studies, vinorelbine appears to be more active than vinblastine and vincristine in both murine tumors and human tumor xenografts.[13] Pharmacokinetic studies indicate intense tissue uptake, especially in lung tissue, and other preclinical data suggest less neurotoxicity because it spares the axonal microtubules compared with the other vinca alkaloids.[14] In phase I studies, the maximum tolerated dose ranged from 27.5 to 35.4 mg/m^2 when given as a weekly intravenous administration, with leukopenia proving to be the dose-limiting toxicity among heavily pretreated patients. Mild peripheral neuropathy has been observed at higher dose levels.[15]

The excellent activity of vinorelbine against NSCLC has been demonstrated in phase II studies. French investigators reported an objective response rate of 29% in 78 chemotherapy-naive patients given a weekly vinorelbine dose of 30 mg/m^2.[15] Similarly, Japanese investigators[16,17] treated 72 patients with advanced NSCLC with 20 and 25 mg/m^2 of vinorelbine per week and observed objective response rates of 26% and 44%, respectively, in chemotherapy-naive patients. An additional 80 chemotherapy-naive patients were treated with the higher vinorelbine dose and confirmed an excellent objective response rate of 33%.

The single-agent activity of vinorelbine, as well as its activity in combination with cisplatin, has been extensively evaluated in randomized phase III trials with positive results.[18-21] In a study designed to obtain approval by the Food and Drug Administration for the single agent in the United States, Crawford and colleagues[20] compared vinorelbine to 5-fluorouracil plus leucovorin in a prospective trial involving 216 stage IV NSCLC patients. Among the patients given vinorelbine, the median survival was 30 weeks with a one-year survival of 25%. Patients treated with 5-fluorouracil experienced a median survival of 22 weeks and a 16% one-year survival; these differences were statistically significant (log rank P=0.03).

French investigators compared single-agent vinorelbine to two combination chemotherapy regimens: cisplatin plus vindesine and cisplatin plus vinorelbine.[18] The single-agent vinorelbine arm and the cisplatin/vindesine arm yielded comparable median survivals of 31 and 32 weeks, respectively. Median survival in the group treated with cisplatin plus vinorelbine was 40 weeks, a statistically superior outcome. In a related study,[21] Southwest Oncology Group investigators compared single-agent cisplatin to vinorelbine plus cisplatin. As in the French trial, the combination arm yielded a superior one-year survival compared to that achieved with the single agent alone (33% vs 12%). Taken together, these data indicate vinorelbine is active against advanced NSCLC and that cisplatin plus vinorelbine is superior to either vinorelbine or cisplatin alone (Table 1). For completeness, it must be noted that a second randomized French trial failed to demonstrate a survival advantage for cisplatin plus vinorelbine compared to vinorelbine alone in advanced NSCLC, although both the objective response rates and the median time to tumor progression favored the combination regimen.[19]

Table 1. – Phase III Trials With Vinorelbine

	Institute Gustave Roussy[18]		Southwest Oncology Group[21]	
	VNB	CDDP + VNB	CDDP	CDDP + VNB
Number of Patients	206	206	218	214
Response	15%	30%	10%	25%
Median Survival	31 wks	40 wks	26 wks	30 wks
1-Yr Survival	25%	35%	12%	33%

VNB = vinorelbine
CDDP = cisplatin

Paclitaxel

Paclitaxel (Taxol) is a member of a new class of agents referred to as the taxanes. Paclitaxel was originally extracted from the bark of the Pacific yew tree, *Taxus brevifolia*. Taxanes effect cytotoxic activity via polymerization and stabilization of microtubules in contradistinction to the classic spindle poisons, vincristine and vinblastine.[22] The exact means by which this activity causes cytotoxicity is unknown, although microtubules are known to be important in numerous cellular activities including mitosis, cell motility, signal transduction, and intracellular transport. Resistance to paclitaxel appears to be due to its function as a substrate for the P-glycoprotein or due to the fact that some tumors contain alpha- and beta-tubulin with impaired ability to polymerize into microtubules.[22] Because cells are arrested in the G_2/M phase of the cell cycle, paclitaxel also serves as an excellent radiation sensitizing agent.[23] Cells arrested in the G_2/M phase are more sensitive to the DNA damaging effects of gamma-irradiation.

In phase I trials, the dose-limiting toxicity of paclitaxel proved to be neutropenia.[22] However, hypersensitivity reactions also were common prior to changing to a 24-hour infusion administration schedule. The neutropenia accompanying paclitaxel is dependent on both dose and schedule and is greater in individuals receiving higher doses or longer infusions. Without hematopoietic growth factors, the maximum tolerated dose of paclitaxel given over 24 hours is between 175 and 200 mg/m^2. With the addition of a hematopoietic growth factor, a dose of 250 mg/m^2 over 24 hours can be administered without major hematologic complications. More recently, shorter infusions of paclitaxel have been studied and found to be well tolerated. The toxicity profile changes somewhat, with neurotoxicities becoming more common and myelosuppression less common.[24]

Due to a limited drug supply, the earliest paclitaxel NSCLC phase II trials included only a small number of patients. Furthermore, to maximize the likelihood that activity would be identified if it existed, the initial phase II trials employed maximally tolerated doses (200 to 250 mg/m^2) given as a 24-hour infusion.[25,26] Eastern Cooperative Oncology Group (ECOG) investigators reported a 21% response rate among stage IV NSCLC patients. Although median survival was similar to that obtained in previous studies of phase II agents carried out within ECOG, one-year survival was approximately twice the usual one-year survival rate (40%). These results, coupled with nearly identical results obtained by investigators at M.D. Anderson Cancer Center, prompted ECOG to undertake further phase II and III studies of paclitaxel in NSCLC (vide infra).

The issue of proper scheduling of paclitaxel is as much a practical and economic one as it is a scientific issue. Given the apparent schedule dependency of paclitaxel in preclinical studies,[27,28] it is reasonable to assume that longer infusions of paclitaxel might be therapeutically superior to short infusion schedules. However, recently completed phase II trials indicate that a shortening of paclitaxel administration does not compromise efficacy in NSCLC [29-31] (Table 2). Indeed, some investigators have used an even shorter infusion rate of one hour with equally encouraging results.[32] On a precautionary note, however, Australian investigators administered paclitaxel over three hours to 51 chemotherapy-naive patients and observed an unimpressive 10% response rate.[33] These investigators used a lower dose of paclitaxel (175 mg/m^2) than was used in the aforementioned phase II trials, which may account for their findings. Although the confidence intervals of all the above phase II trials overlap, these findings suggest a possible dose-response relationship (or at least a "threshold" effect) might exist for paclitaxel in NSCLC. The existence of a dose-response relationship requires prospective determination.

Table 2. – Phase II Trials of Paclitaxel in Non-Small-Cell Lung Cancer

Author	Schedule	Dose (mg/m^2)	Response	% Response
Chang et al[25]	24 hr	250	5/24	21
Murphy et al[26]	24 hr	200	6/25	24
Gatzemeier et al[29]	3 hr	225	8/37	22
Tester et al[31]	3 hr	200	6/19	32
Millward et al[28]	3 hr	175	5/51	10
Sekine et al[30]	3 hr	210	23/60	38
Hainsworth et al[32]	1 hr	135-200	7/27	26
Totals		135-250	60/243	24.6

Preclinical studies suggest paclitaxel and cisplatin possess additive or even synergistic cytotoxicity.[34] Johns Hopkins investigators initiated phase II trials with this combination and reported that a paclitaxel dose of 135 mg/m^2 administered over 24 hours could be given safely with cisplatin without hematopoietic growth factors.[35]

With granulocyte colony-stimulating factor (G-CSF), the dose of paclitaxel could be escalated to 250 mg/m^2.[36] Based on these data, ECOG investigators undertook a phase III trial (E5592) in which cisplatin and paclitaxel at two dose levels were compared to cisplatin and etoposide, a "standard" combination regimen commonly used in the treatment of advanced NSCLC. Cisplatin and paclitaxel yielded a higher objective response rate compared to cisplatin and etoposide. However, there was *not* an obvious dose response with paclitaxel.[37] More important, survival was superior in the paclitaxel-treated populations. In contrast, European investigators compared cisplatin and paclitaxel to cisplatin and teniposide and failed to observe a survival benefit with the paclitaxel-containing regimen, although the response rate was superior to the teniposide regimen.[38]

Another regimen with promising activity against advanced NSCLC is carboplatin plus paclitaxel.[39-42] Several investigators have demonstrated good overall response rates and improved median survival in nonrandomized trials. Whether this regimen is superior to cisplatin plus paclitaxel will be determined upon completion of a recently activated phase III trials. Finally, paclitaxel is also being studied in combination with ifosfamide, vinorelbine, and gemcitabine.

Docetaxel

Docetaxel (Taxotere), an analog of paclitaxel, is obtained by semisynthesis from 10-deacetyl baccatin III, extracted from the needles of the European yew tree *Taxus baccata*.[43] Like paclitaxel, docetaxel exerts its cytotoxic effect through the inhibition of microtubule depolymerization and promotion of microtubule assembly. In preclinical studies, docetaxel has proved to be more active as a promoter of tubulin polymerization and is more than twice as potent as paclitaxel in inhibiting the replication of J774.2 and P388 cells.[44,45] Its activity is broad and comparable to that of paclitaxel, albeit seemingly more potent in some instances.[45-48] Like paclitaxel, docetaxel has potent radiation-sensitizing properties.

Dose-dependent neutropenia proved to be the dose-limiting toxicity of docetaxel in phase I trials. Unlike paclitaxel, the neutropenia is not schedule dependent.[43] Additional toxicities include hypersensitivity reactions and cutaneous reactions principally manifested as a maculopapular rash or erythema that occasionally progressed to edema and desquamation. Nausea and emesis are sufficiently uncommon that routine antiemetic therapy is not recommended for individuals receiving single-agent docetaxel. Neurotoxicity, manifested as numbness that is mild and reversible, is not common with docetaxel. Cardiac toxicity is also relatively uncommon. Asthenia seems to be more common with docetaxel compared to paclitaxel, although no direct comparison data are available. The recommended phase II dose of docetaxel is 100 mg/m^2 administered over one hour and repeated every 21 days. However, this dose may be unnecessarily high as several recent trials indicate that lower doses are effective and considerably less toxic.

Table 3. – Phase II Trials of Docetaxel in Non-Small-Cell Lung Cancer

Author	Schedule	Dose (mg/m^2)	Response	% Response
Fossella et al[49]	1 hr	100	13/41	33
Francis et al[50]	1 hr	100	11/29	38
Cerny et al[51]	1 hr	100	8/35	23
Burris et al[52]	1 hr	100	3/14	21
Miller et al[53]	1 hr	75	5/20	25
Totals		75-100	40/139	29

Phase II trials of docetaxel in chemotherapy-naive NSCLC patients are summarized in Table 3.[49-53] In all but one of the studies, investigators used 100 mg/m^2 every 21 days. Investigators at Memorial Sloan-Kettering Cancer Center also evaluated a slightly lower dose of docetaxel (75 mg/m^2) in an attempt to lower toxicity.[53] In all studies, the principal toxicity proved to be myelosuppression, although rash and fluid retention were common. Hypersensitivity reactions or allergic reactions were also common but rarely precluded treatment. Overall response rates ranged from 23% to 38%.

Based on these limited data, there does not appear to be an obvious dose response in NSCLC. However, investigators at Memorial Sloan-Kettering Cancer Center recommend using the higher docetaxel dose in future NSCLC studies.[53] This recommendation was made largely because the toxicity of the lower dose of docetaxel (75 mg/m^2) was comparable to that of the higher dose (100 mg/m^2) in their hands. Japanese investigators have found lower doses of 60 mg/m^2 yield response rates in breast cancer equivalent to that achieved with the higher docetaxel doses. Extrapolating to lung cancer seems reasonable, and the study of optimal dose is ongoing.

Initial combination chemotherapy trials using docetaxel have been limited to cisplatin-based regimens.[54,55] Overall response rates and preliminary survival data are encouraging. However, it is clear that hematologic and nonhematologic toxicities are substantial even with reduced doses of docetaxel. Unlike paclitaxel, the effect of drug sequence has not been adequately evaluated. With paclitaxel, host toxicity is reduced when paclitaxel precedes cisplatin.[35] Although only a few groups have attempted to combine docetaxel with drugs other than cisplatin, preclinical data suggest docetaxel should be explored in combination with vinorelbine, another microtubule poison with excellent activity against NSCLC.[56] ECOG is conducting a phase III trial in which cisplatin plus paclitaxel is being compared to docetaxel plus cisplatin. The dose of docetaxel plus cisplatin is 75 mg/m^2. In the paclitaxel arm, cisplatin is 75 mg/m^2 and the paclitaxel dose is 135 mg/m^2 over 24 hours based on the results of ECOG trial E5592.

Table 4.– Taxanes in Platinum-Resistant Non-Small-Cell Lung Cancer

Author	Drug	Dose (mg/m^2)	Schedule	Number of Patients	% Response	Survival
Fossella et al[59]	Docetaxel	100	1 hr	44	21	42 wks
Murphy et al[58]	Paclitaxel	175	24 hr	40	3	ns
Ruckdeschel et al[60]	Paclitaxel	200-250	24 hr	14	14	ns
Hainsworth et al[32]	Paclitaxel	200	1 hr	16	38	ns

ns = not significant

Second-line chemotherapy for previously treated NSCLC is not routinely recommended as virtually no drug is capable of effecting tumor regression in this setting.[57] However, the availability of new drugs with unique mechanisms of action has prompted investigators to assess the activity of these agents in previously treated patients. Investigators at M.D. Anderson Cancer Center administered paclitaxel and docetaxel to NSCLC patients who *failed* front-line cisplatin-based chemotherapy.[58,59] The results of the two trials are summarized in Table 4. In the docetaxel trial, 44 patients were included, 36 of whom had failed to respond to previous chemotherapy. Eighteen of the patients had received two prior chemotherapy regimens. Surprisingly, docetaxel yielded an overall response rate of 21% and a median survival of nearly 10 months. For comparison purposes, a review of the ECOG experience in NSCLC indicates that survival after recurrence following cisplatin-based chemotherapy is typically just three months. An attempt to replicate these remarkable results is currently underway in an ongoing phase III trial in which patients with recurrent or relapsed NSCLC are randomized to docetaxel, vinorelbine, or ifosfamide. Interestingly, these same investigators were unable to demonstrate a similar level of activity in recurrent or relapsed NSCLC with paclitaxel. Among 40 patients who failed cisplatin-based chemotherapy, only 3% had an objective response to paclitaxel at a dose

of 175 mg/m^2 by 24-hour infusion (no survival data were provided). However, other investigators have reported good activity in platinum-resistant patients.[32,60] Finally, preclinical data indicate that docetaxel is not completely cross-resistant to paclitaxel. Thus, it is conceivable that these agents may be useful in combination or sequentially.

Gemcitabine

Gemcitabine (Gemzar) is an analog of the pyrimidine anti-metabolite cytosine arabinoside (Ara-C). Its cytotoxic effect is caused by the competitive incorporation of phosphorylated gemcitabine into DNA. The activity of gemcitabine in solid tumors may be related to its accumulation within tumor cells at much higher levels and for longer intervals than the active metabolite of Ara-C.[61,62] Gemcitabine triphosphate also inhibits the deaminase responsible for its degradation, thus leading to "self potentiation."[63]

In phase I trials, gemcitabine has been shown to exhibit schedule-dependent cytotoxicity. Weekly administration of gemcitabine appears to be the most efficacious schedule. The maximum tolerated dose was 790 mg/m^2, with myelosuppression as the dose-limiting toxicity. Additional side effects included a flu-like syndrome, fever, hypotension, and occasionally liver toxicity (ie, mildly elevated transaminases). Less frequent side effects were rash, edema, shortness of breath, and proteinuria.

Table 5. – Gemcitabine (2', 2'-difluorodeoxycytidine) in Non-Small-Cell Lung Cancer

Author	Dose (mg/m^2)	Schedule	Number of Patients	CR + PR	% Response
Abratt et al[64]	1,000-1,500	day 1, 8, 15	76	15	20
Anderson et al[65]	800-1,000	day 1, 8, 15	79	16	20
Shepherd[66]	1,250-2,100	day 1, 8, 15	93	19	20
Negoro et al[67]	1,000-1,250	day 1, 8, 15	74	20	27
Begbie et al[68]	1,250	day 1, 8, 15	29	6	21
Fossella et al[67]	1,000-1,750	day 1, 8, 15	19	4	21
Totals	800-1,750		370	80	22

CR = complete response
PR = partial response

Table 5 lists the published phase II trials employing gemcitabine in NSCLC.[64-67] Most trials employed a weekly-times-three regimen repeated every 28 days with a dose range of 800 to 2100 mg/m^2. The response rates in previously untreated NSCLC range from 20% to 28% and do not appear to be dose related. For example, Anderson et al[65] treated 82 patients with gemcitabine at two dose levels: 800 and 1000 mg/m^2. Of the 79 evaluable patients, 16 (20%) achieved a partial response. Of the 27 patients who received the higher gemcitabine dose, only two (7%) achieved a partial response, whereas among the 52 patients given gemcitabine at 800 mg/m^2, 14 achieved a partial response for an overall response rate of 27%. Early results in small-cell lung cancer also are promising, although the overall experience in this disease is limited.[68]

In preclinical studies, gemcitabine has demonstrated synergistic cytotoxicity with several drugs, including cisplatin and etoposide.[69,70] The mechanism of this synergy is not well defined but may involve inhibition of DNA repair caused by DNA-damaging agents such as cisplatin.[71] It is well known that some lung cancer cell lines express high levels of p185^{neu}. These particular cell lines appear to be more effective at repairing DNA damage caused by cisplatin and, in turn, are not killed as effectively as cell lines that do not overexpress p185^{neu}. Preclinical data indicate that a combination of cisplatin and gemcitabine may be more active against NSCLC tumors that overexpress p185^{neu} than many currently used combinations,[71] thus suggesting that additional study in the clinical arena of this regimen is warranted. Phase I/II trials of cisplatin and gemcitabine are underway with preliminary results yielding promising rates of response.[72-79] ECOG investigators are prospectively comparing cisplatin plus gemcitabine to cisplatin plus paclitaxel, the current "standard" regimen in ECOG for NSCLC.

Camptothecins

In 1958, extracts from the leaves of the native Chinese tree, *Camptotheca accuminata*, were found to exhibit antitumor activity in vitro.[80] A plant alkaloid, camptothecin, was eventually purified from these extracts and entered phase I testing in the late 1960s. Although modest antitumor activity was demonstrated in the early clinical trials, the drug was largely rejected for further development because of intolerable side effects, the most notable being unpredictable and severe cystitis and myelosuppression. Despite these potential drawbacks, some pharmaceutical companies continued the study of the camptothecins. These efforts eventually led to the discovery of two water soluble camptothecin derivatives: irinotecan (CPT-11, Camptosar) and topotecan (Hycamtin). In the mid 1980s, camptothecin was found to exert its antitumor activity through a mechanism that involved the nuclear enzyme, topoisomerase I.[81] This discovery, together with the promising results from early clinical trials of irinotecan and topotecan, led to renewed interest in the camptothecins (Table 6).

Table 6. – Topoisomerase I Inhibitors in Non-Small-Cell Lung Cancer

Author	Drug	Dose	Number of Patients	% Response
Lynch et al[82]	Topotecan	2 mg/m^2/d X 5 q 3 wk	20	0
Perez-Soler et al[83]	Topotecan	1.5 mg/m^2/d X 5 q 3 wk	48	15
Weitz et al[84]	Topotecan	1.5 mg/m^2/d X 5 q 3 wk	38	18
Weitz et al[84]	Topotecan	1.3 mg/m^2/d X 3 q 3 wk	40	8
Fukuoka et al[90]	Irinotecan	100 mg/m^2 q 1 wk	73	32
Negoro et al[89]	Irinotecan	100 mg/m^2 q 1 wk	67	34
Douillard et al[91]	Irinotecan	350 mg/m^2 q 3 wk	11	36

Two published phase II trials[82,83] reported on the use of topotecan in patients with chemotherapy-naive advanced NSCLC. Lynch and colleagues[82] invoked an early stopping rule in their phase II trial because no responses were observed in the first 20 enrolled patients. Despite the lack of a single objective response, median survival was reported to be 7.6 months. The authors attributed this surprisingly prolonged survival to patient selection or perhaps a disease stabilization effect by topotecan. A similar trial was reported by Perez-Soler and colleagues[83] in which an overall response rate of 15%, median survival of 8.9 months, and one-year survival rate of 30% were observed. The authors noted that their response rate was 36% (5/14) in patients with squamous cell carcinomas vs only 4% (1/26) in patients with nonsquamous histologies. They also noted that the study by Lynch and colleagues[82] included only three patients with squamous cell carcinoma, possibly indicating that activity was

limited to this histology. The preliminary results of a large randomized phase II trial comparing two different schedules of topotecan in advanced NSCLC indicate that there is no significant difference in activity in patients with squamous vs nonsquamous histologies.[84] Median survivals were reported as 8.4 vs 6.0 months for a conventional schedule of five consecutive days vs a schedule of three-day continuous infusion. Although median survivals are similar to those observed with other newer agents, the enthusiasm for the continued development of topotecan in advanced NSCLC has been limited because of the modest response rates observed in phase II trials.

Unlike topotecan, irinotecan effected high response rates in phase I and early phase II trials in advanced NSCLC and small-cell lung cancer.[85-91] Fukuoka and colleagues described the results of a phase II study of single-agent irinotecan in 73 patients with advanced and chemotherapy-naive NSCLC.[90] Irinotecan was administered at 100 mg/m^2 per week, and an overall response rate of 32% and a median survival time of 9.8 months were observed. Grade 3 and 4 toxicities included leukopenia (25%), diarrhea (21%), nausea/vomiting (22%), anemia (15%), alopecia (4%), and pneumonitis (3%). Patients did not routinely receive antiemetics and antidiarrheal medications. Other groups have confirmed this high level of activity.

Recent biological studies have indicated that topoisomerase I may have a role in the subsequent DNA degradation and cell death that follow DNA damage from other sources.[18] Furthermore, camptothecin appears to enhance this process by stimulating the DNA-cleaving activity of the enzyme. Preclinical murine lung cancer models demonstrate therapeutic synergy when irinotecan is used in combination with cisplatin, another DNA-damaging agent.[92] Because cisplatin is a staple in the management of NSCLC, it is logical to combine these two agents in the treatment of this disease. To this end, Masuda and colleagues[93] conducted a phase I/II trial of irinotecan and cisplatin in patients with advanced NSCLC. Cisplatin doses were fixed at 80 mg/m^2 and given on day 1 of each four-week treatment cycle. Irinotecan doses were gradually escalated and given on days 1, 8, and 15. The recommended phase II doses were cisplatin at 80 mg/m^2 on day 1 and irinotecan at 60 mg/m^2 on days 1, 8, and 15. Dose-limiting toxicities included diarrhea and neutropenia. The response rate was 54%. Survival data were not available.

Given the early favorable results from the phase I trial of Masuda and colleagues, a multicenter US phase II trial of their regimen was undertaken, and preliminary results are now available (R.F.D., unpublished data, 1997). Among the 52 patients treated, there was a response rate of 31% and a median survival of 8.4 months. Grade 3/4 toxicities included neutropenia (46%), thrombocytopenia (12%), anemia (8%), nausea (33%), asthenia (21%), late diarrhea (17%), and dehydration (10%). Toxicities were typical of cisplatin-based chemotherapy except for diarrhea, which is peculiar to irinotecan. The trial was considered flawed because cisplatin doses were fixed and not adjusted for toxicity. Several patients had irinotecan dose reductions for toxicities typically attributed to cisplatin. Given the high incidence of irinotecan dose reductions (73%), most patients received irinotecan doses of one third or less that of conventional single-agent doses. Moreover, the majority of irinotecan doses were given on days in which cisplatin was not administered (days 8 and 15). Therefore, this trial appeared suboptimal as an attempt to explore the therapeutic synergy of these agents that theoretically would require same-day administration of both drugs.

In an attempt to develop a regimen in which irinotecan and cisplatin are administered concurrently, Saltz and colleagues[94] at Memorial Sloan-Kettering Cancer Center recently completed a phase I trial of weekly cisplatin and irinotecan. Activity was observed in patients with esophageal cancer and NSCLC. A phase II trial of this regimen is currently underway in patients with advanced NSCLC. Theoretically, therapeutic synergy should be optimized by administering the irinotecan immediately following cisplatin while simultaneously reducing host toxicity. Unnecessary dose reductions will be avoided.

Conclusions

These new agents ensure that a proliferation of new studies in lung cancer will be forthcoming over the next several years. Optimistically, these agents may modestly improve survival in this devastating disease. However, their greatest benefit may be their favorable toxicity profiles. In other words, even if survival benefits are marginal, the lower toxicity associated with many of the newer drugs may result in an overall net benefit for patients with incurable disease.

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