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SMALL CELL LUNG CANCER: CURRENT THERAPY AND PROMISING NEW REGIMENS

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Small cell lung cancer (SCLC) accounts for 15-20% of all lung cancers in the USA. This cell type has the strongest association with cigarette smoking and is rarely observed in someone who has never smoked. SCLC is generally staged as Limited or Extensive stage disease according to the old Veterans Administration Staging System. Limited stage disease is confined to one hemithorax, mediastinum and ipsilateral supraclavicular nodes. It is disease that can be encompassed within one radiation portal. Extensive stage is any disease that has spread beyond these sites. Malignant pleural effusion or contralateral supraclavicular nodes or contralateral hilar nodes are generally considered to be extensive stage disease. Table I outlines the response rates and survival of patients enrolled on phase II and III clinical trials from 1975 to 1990 at Mayo Clinic and in the North Central Cancer Treatment Group (1).

Table I:

	Limited Stage	Extensive Stage
Total number	770	845
Complete response(%)	59	24
Median survival (mo)	15	9
2-year survival (%)	29	8
5-year survival (%)	12	2

Approximately one-third of patients will have limited stage disease and they have a response rate of 80-90% with standard chemotherapy. A complete clinical response can be achieved in 50-60% of patients. In a meta-analysis of trials with chemotherapy alone versus combined with thoracic radiotherapy, survival was significantly better with combined modality therapy.

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Additional chemotherapy beyond 4-6 cycles has not been shown to prolong survival.

Recently, two different cooperative groups randomized patients to once a day versus twice a day thoracic radiotherapy with standard chemotherapy for all patients (2,3). Turrisi et al (2) reported the long-term follow-up of patients enrolled in the ECOG/RTOG trial (Table 2) and concluded that twice a day radiotherapy resulted in a statistically better 5-year survival. All patients received 4 cycles of etoposide and cisplatin chemotherapy (2 concurrent with radiotherapy) and thoracic radiotherapy began on day one of treatment. Bonner and associates (3) reported the NCCTG experience and concluded that there was no difference in survival with twice daily radiotherapy versus once daily therapy. All patients received identical chemotherapy with six cycles of etoposide and cisplatin (Table II). Radiotherapy began with cycle 4 of chemotherapy.

Table II:

Trial Groups	ECOG/RTOG		ECOG/RTOG	
	CT+TRT	CT+twice daily TRT	CT+TRT	CT+twice daily TRT
Number	176	182	133	130
Median survival Time (mo)	18.6	20.3	21	21
2 yr survival (%)	42	44	47	45
3 yr survival (%)	-	-	34	29
5 yr survival (%)	16	26	-	-

What is clear from both studies is that the median survival is now 18-20 months with concurrent chemotherapy and thoracic radiotherapy and 40% of patients will be alive at 2 years. The 5-year survival (cure rate) is 15-25%. It is unclear if twice daily thoracic radiotherapy is superior to standard once daily radiotherapy, but local recurrence is still a problem in over 50% of individuals with doses of thoracic radiotherapy less than 50 Gy.

TREATMENT OF EXTENSIVE STAGE

In the late 1960s and early 1970s, new chemotherapeutic agents were identified that had single agent activity against small cell lung cancer with

response rates of 30% or greater. Subsequent trials in the early 1970s established (cyclophosphamide, doxorubicin, and vincristine [CAV]) as an effective therapy. The first effective second-line therapy was with etoposide and cisplatin (EP) and was reported in the mid 1980s.

Two cooperative oncology groups carried out randomized prospective trials evaluating CAV versus EP versus alternating CAV and EP (4,5). These trials showed similar survival on all three arms for extensive stage patients. The myelosuppression and other toxicity associated with the CAV regimen was greater and subsequently EP was adopted as standard therapy in the United States.

Subsequently, trials have been performed looking at a variety of combination chemotherapeutic agents against extensive stage small cell lung cancer. The CAE regimen (cyclophosphamide, doxorubicin and etoposide) has been a commonly used regimen in European trials. The other commonly used combinations are etoposide and carboplatin (EC), etoposide, ifosfamide, cisplatin (VIP), and ifosfamide, carboplatin, etoposide (ICE). The median survival with all these regimens is in the 8-10 month range with two-year survival of 10% or less. No regimen has been shown to be superior to etoposide/cisplatin or etoposide/carboplatin.

NEW AGENTS

In the 1990s a number of promising new agents have entered into clinical trials. Paclitaxel was tested by ECOG and NCCTG in previously untreated small cell lung cancer with response rates of 34% and 68%, respectively, demonstrating activity of this agent in previously untreated small cell lung cancer (6). The ECOG evaluated topotecan at a dose of 2.0 mg/m2 x5 in untreated small cell lung cancer and observed a response rate of 39% (7). Japanese investigators have evaluated CPT-11, another topoisomeraseI inhibitor, and demonstrated activity of this agent against small cell lung cancer. Recently, in a trial at the University of Pittsburgh, topotecan and paclitaxel was evaluated in untreated extensive disease small cell lung cancer patients. All patients received G-CSF support. Twenty-nine patients were enrolled on study and 28 patients were evaluable. There were 17 major responses (6 CR and 11 PR) for a response rate of 60% (8). The median survival time was 54 weeks with one and two year survival rates of 50% and 15%. Toxicity was predictable and was primarily myelosuppression.

At the ASCO 2000 meeting, the CALGB reported the results of their Phase II trial topotecan and paclitaxel with G-CSF support. They administered the paclitaxel by 3-hour infusion on day one followed by topotecan daily for 5 days (9). They treated 34 evaluable patients and had 1 CR and 22 PR for an overall response rate of 68%. The median survival time was 9.4 months and the estimated one-year survival was 26%. They concluded that the combination of paclitaxel and topotecan was no better than standard therapy. Also at ASCO 2000, the North Central Cancer Treatment Group reported the results of their trial of alternating chemotherapy with paclitaxel/topotecan and etoposide/cisplatin. Of 46 evaluable patients there was a major response in 76% (10). The median survival time was 10.5 months and the one-year survival was 38%. While these results were good, they were not obviously superior to standard therapy.

ECOG reported a trial for extensive stage small cell lung cancer patients. All patients received 4 cycles of etoposide and cisplatin and then were randomized to observation alone or further treatment with 4 cycles of single-agent topotecan. The median survival from the second randomization was essentially identical with a median survival of 8.9 months (observation) and 9.3 months (topotecan). Quality of life was not significantly improved with topotecan and toxicity was considerably greater (11).

The most exciting ASCO 2000 abstract on small cell lung cancer was the report by Noda et al (11). The JCOG Phase III trial compared CPT-11 and cisplatin versus etoposide and cisplatin in extensive stage disease patients. The overall response rate with CP vs EP was 89% vs 67%. The MST and one-year survival with CP was 420 days and 60% versus 300 days and 40% with EP. (P = .005) Myelosuppression was somewhat greater following EP (P = .01) and grade III-IV diarrhea was greater after CP (P = .0001). A Confirmatory Phase III trial is being planned by SWOG.

PROPHYLACTIC CRANIAL IRRADIATION

Prophylactic cranial irradiation (PCI) is one of the most controversial areas in treatment of small cell lung cancer. If a patient achieves a complete remission then there is a 50% chance of developing cranial metastasis within the next two years. Small randomized trials have shown that PCI significantly reduces the rate of CNS metastases when compared to those who do not receive PCI. There have also been reports in the literature of neurocognitive abnormalities and neurologic sequelae, such as ataxia, that have developed as a result of PCI.

Recently, a meta-analysis was performed of seven randomized trials of PCI vs no PCI of patients in complete remission. The authors observed a beneficial effect after PCI with 5.4% increase in absolute survival at 3 years (13). The major questions raised by the meta-analysis concern the optimal dose and sequencing of PCI. Advocates of PCI point out two trials in Europe that prospectively performed neuropsychiatric testing in patients on randomized trials of PCI or no PCI. They did not observe any significant increase in neuropsychologic symptoms, nor increased cortico-atrophy or ventricular dilatation as evaluated by CT (14,15). Detractors argue that these trials were suboptimal and that more data is needed. In practice, experts vary in their recommendation on the use of PCI.

SECOND LINE THERAPY

When patients relapse after initial therapy, the median survival time is generally 3-4 months. The longer the patient has been in remission, the more likely they are to respond to second-line therapy. In patients who have been off treatment for six months or more, it is reasonable to retreat them with the same initial agents that have achieved the first remission. The chance of a second response is approximately 50%. If a patients have not been treated with a platinum-based regimen, then second-line therapy should include a platinum regimen such as EC or EP.

A number of clinical trials have evaluated topotecan as second-line therapy in patients with relapsed small cell lung cancer. If a patient had responded to initial therapy and has been off chemotherapy for three months or longer then their response to second-line topotecan has been approximately 25-35% (16). Recently, topotecan was approved by the FDA for second-line treatment of small cell lung cancer. If a patient relapses while on therapy or has been off therapy less than 2-3 months, their response to topotecan or any other chemotherapy regimen is generally <10%. The NCCTG is currently conducting a second line therapy trial for progressive or relapse small cell. Patients receive topotecan (1.25 mg/m2) daily for 3 days and paclitaxel (200 mg/m2/3 hrs) on day 3. G-CSF support is not used for the initial cycle. This trial is currently open and has accrued 60 patients. In summary, patients with extensive stage small cell lung cancer have a 75-85% response rate to initial chemotherapy. The median survival time is 8-9 months and the two-year survival is <10% and there are virtually no five-year survivors. A recent review by the National Cancer Institute-Navy, was unable to substantiate any improvement in survival with small cell lung cancer since the mid 1970s (17). New agent therapies are desperately needed for treatment against small cell lung cancer.

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