Discussion: Evaluation of Current Clinical Status and Future Directions in Small Cell Lung Cancer

Dose Intensity

Dr. Bunn: Perhaps we might start by focusing on dose intensity. Dr. Ihde from the National Cancer Institute reported on small cell lung cancer patients who received what he considered to be the standard dose of etoposide and cisplatin, which at the National Cancer Institute is 80 mg/m^2/day of intravenous etoposide for 3 days and 80 mg/m^2 of cisplatin on day 1. No improvement in response rate or survival was seen when patients received a dose increase of approximately 40%. However, toxicity, particularly myelosuppression, increased. If one were to compare his therapeutic and toxicity results with those of any study using a growth factor, Ihde’s study had comparable therapeutic results but less toxicity. Fewer than 10% of patients had grade 4 neutropenia. Fewer than 5% of patients were hospitalized for febrile neutropenia. Even in the control arms of the CAE-plus-growth-factor trials, 30% of patients required hospitalization for febrile neutropenia.

My question is, are we correct in intensifying dose and administering growth factors? Dr. Bishop, do you have any evidence that increasing the carboplatin or etoposide dose and adding growth factor to the regimen will lead to a higher response rate or longer survival?

Dr. Bishop: At this time, we do not have any evidence of increased efficacy, although the numbers of patients are too small to be definite. The results for the higher double dose of carboplatin and etoposide look similar to those from our large cohort of patients who have received standard-dose carboplatin and etoposide over the years. The question of dose intensity is under scrutiny.

Dr. Johnson: We need to make some distinctions when we talk about dose intensity. What we are talking about in some instances is dose escalation, dose response, and dose intensity. Clearly, tumors like small cell lung cancer show a dose-response curve for a number of agents, most notably the alkylating agents. For example, in England, it has been reported that a large, single dose of cyclophosphamide, 7 g/rrr, was effective in achieving response in 80% of patients. A single cyclophosphamide dose produced survival rates similar to those achieved with multiagent therapies.

Dose intensity, on the other hand, is different. As Dr. Greco noted, the total dose that one administers may be similar or identical, yet the dose intensity may be different, depending on how one administers the drug. I do not believe that we’ll be able to dose escalate to a meaningful degree in patients with small cell lung cancer, who have a median age of 60 years in most trials. The nonhematologic toxicities will be the limiting factor. Furthermore, since even in the most chemoresponsive neoplasm, namely, testicular cancer, randomized dose escalation trials have not demonstrated benefit, I question whether we can achieve a benefit in a less responsive neoplasm. Dose intensity may be more possible when growth factors are also administered. Certainly, Dr. Masuda’s presentation on CODE with daily G-CSF indicates that this may be one route to pursue. Nevertheless, the data demon-
strated 12-month median survival – which is precisely what we achieved with our dose-intense, escalated-dose CEP regimen with only two cycles of therapy. The difference was that Dr. Masuda’s group administered therapy on an outpatient basis, whereas our patients were hospitalized.

I am not particularly optimistic that the kinds of dose escalations we see when using growth factors – namely, etoposide dosages of 200, 250, or even 300 mg/m2/day -are likely to make a meaningful overall difference. To achieve these differences, we are going to have to use gram levels, but I do not think that the growth factors are going to allow us to do that, based on what we have seen so far.

Growth Factors
Dr. Bunn: Should growth factors be used if and when a patient becomes neutropenic rather than prophylactically in every patient? There have not been any published randomized trials in the United States that compared G-CSF or GM-CSF to placebo in patients who became neutropenic and/or febrile. Apparently, in an Australian trial, patients are being randomized to receive G-CSF or placebo if they develop febrile neutropenia. Dr. Bishop, can you comment on that trial?

Dr. Bishop: In an ongoing, randomized trial, patients who develop febrile neutropenia (< 1,000 neutrophils) with temperatures above 38 °C and who require antibiotics are treated with either G-CSF or placebo. We expect to complete the study in September 1991 and will report the results at the end of the year or early in 1992.

Dr. Wolf: We have studied the use of GM-CSF after dose escalation with etoposide and cisplatin in small cell lung cancer. The starting dose for cisplatin was 90 and 150 mg/m2 for etoposide for 3 days. When we escalated the doses in 50-mg increments, we were only able to go as high as 200 mg. At 250 mg, severe neutropenia occurred in most patients. The only difference noted was that the duration of neutropenia, but not the degree, was markedly shortened in the GM-CSF group compared with the placebo group.

Dr. Bishop: One of the most interesting aspects about growth factors is their ability to expand the progenitors in peripheral blood and demonstrate some differences in the early progenitors associated with these expansions. If we can identify the progenitors and use appropriate combinations of growth factors to expand, harvest, and then transplant the progenitors with peripheral stem cells, we might be able to intensify treatment to the four to six times required for appropriate dose intensification with minimal myelosuppression. We have already reduced the neutropenic period from an average of about 18 days to 8 or 9 days using GM-CSF or G-CSF. With progenitor expansions and more understanding of growth factor combinations, we may be able to reduce the neutropenic period even further.

Etoposide Schedules
Dr. Bunn: Prolonged etoposide administration might be a more appropriate therapeutic strategy in small cell lung cancer. Dr. Greco, do you feel comfortable giving single-agent oral etoposide for either 14 or 21 days to an elderly or unfit patient with small cell lung cancer?

Dr. Greco: It’s reasonable, considering the relative lack of toxicity and high response rate. Prolonged administration of etoposide alone may be as effective as combination chemotherapy. It might be worthwhile to study etoposide at lower doses for an even longer time.

Dr. Bunn: On the other hand, Dr. Bishop’s studies showed that the elderly fared just as well with a little more toxicity, but their outcome was the same. Dr. Gatzemeier, have you looked at patients more or less than 70 years old to determine if the addition of platinum might affect patients differently according to age?
Dr. Gatzemeier: We did not look at age specifically, but we have experience with a group of elderly patients treated with oral etoposide for 3 days, followed by 7 days’ rest, and then 3 days of treatment. The remission rate was about 65%, which is similar to the survival and remission duration we had with combination therapy. In elderly or unfit patients, I think oral etoposide is a good alternative to combination chemotherapy, but we need randomized trials to determine whether it is more effective than combination chemotherapy.

Dr. Bunn: Dr. Masuda, can elderly patients tolerate the CODE regimen?

Dr. Masuda: We use CODE therapy in patients up to age 75. When subjecting patients to weekly chemotherapy, we must be concerned about constitutional symptoms like myelosuppression. In Japan, we have not encountered major problems in patients 75 or younger. When performance status deteriorates, dose intensity becomes a problem. Thus, we have to maintain performance status at 0-2.

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Dr. Johnson: The Canadian CODE study initially included patients up to age 75, but the cutoff age was changed to 65. The investigators’ clinical impression was that patients older than 65 years had a difficult time completing the entire course of chemotherapy. If a randomized trial were undertaken in North America, the Canadians would probably request that the patients be carefully selected to include those under age 65 and with a performance status of 0-1.1, however, think that, as long as performance status requirements are met, patients up to any age could be included in such a trial. If one excludes patients over age 65, then nearly half of the patients in this population would be excluded.

Dr. Bunn: Dr. Masuda, would it be reasonable to give etoposide daily rather than the intermittent 3-times-a-week schedule? Should we incorporate this type of schedule into the CODE regimens?

Dr. Masuda: Chronic, daily etoposide dosing presents a concern about myelosuppression. The dose schedule should be carefully examined when we combine drugs.

Dr. Kunito: I’m impressed by the pharmacokinetic data that Dr. Greco presented. Assuming 90% bioavailability, then 50 mg/day for 21 days equals a total of nearly 1,000 mg per course of etoposide. As Dr. Johnson suggested, I think the data are too sparse to combine large amounts of etoposide into the intensive CODE regimen at this point. Furthermore, using the CODE regimen with chronic, daily etoposide excludes the use of G-CSF. When we used very intensive chemotherapy rather than CODE with daily etoposide and G-CSF administered the same day, no unexpected side effects occurred. Dr. Greco, would you give G-CSF every day along with etoposide?

Dr. Greco: To improve the CODE regimen, which is based on a reasonable premise, you want to decrease toxicity and possibly use other drugs or change the etoposide schedule. Giving G-CSF the day before or after chemotherapy is actually giving it simultaneously. Biologically, missing 1 day is not an issue as the marrow is just as stimulated. We currently use G-CSF with daily etoposide. Preliminary data indicate no increased myelosuppression.

Dr. Johnson: I would like to expand on this a bit. We still are not sure that the extended administration of etoposide is superior to standard 3- to 5-day schedules, since this has not been substantiated prospectively. If we were to modify the CODE regimen, it might be reasonable to consider using very low-dose etoposide for the entire 9 weeks. The 50-mg/m²/day dosage that we have been using is certainly the maximum tolerated dose for the single agent. But that by no means indicates that this is the most effective therapeutic dosage. As Dr. Greco pointed out, 10 mg/m²/day for 50 days may be a more effective way to use etoposide. I believe that the plasma
level necessary to achieve cytotoxicity in small cell lung cancer is around 1 \text{ug/ml}. Inferential and preclinical data support this. Since oral etoposide has a half-life of approximately 6-7 h, we ought to give it at least twice daily. In Slevin’s trial, oral etoposide 50 mg was given twice a day for 14 consecutive days. Our pharmacokinetic studies show that the variations in plasma levels do not seem to relate to the patient’s dose in meters squared. Therefore, a 50-mg dose once or twice a day is probably just as useful. Per-meter-squared dosing is probably not justified, because the 15% or so variability in absorption will counterbalance any fine tuning with the dosing. Etoposide absorption is rapid. Within 1 to 2 h the peak is reached, usually around 3-4 \text{ug/ml} with a 100-mg dose. The level stays above 1 \text{ug/ml} for up to 18 h with once daily dosing. In Slevin’s study using a 50-mg dose, peak levels were approximately 2.5 \text{ug/ml}, and were maintained above 1 \text{ug/ml} for roughly 12 h. If one doses again at 12 h, the peak is not as high, which may be less toxic. The level, however, is maintained at a more constant value for the entire 24 h between roughly 1 and 2.5 \text{ug/ml}.

Dr. Nagata: Dr. Johnson, how do you increase compliance with oral etoposide?

Dr. Johnson: Compliance is not a problem with oral etoposide. Apart from myelosuppression and hair loss, there are remarkably few side effects. One unique toxicity is a slightly increased incidence of diarrhea, which is mild and relatively rare. Nausea and other gastrointestinal side effects are minimal. Although we have not done a placebo-controlled trial, I would guess that the incidence of nausea with placebo would be roughly equivalent to what we see with oral etoposide. Fewer than 10% of patients complain of severe nausea, and vomiting is virtually nonexistent. Minor mucositis has been reported.

To determine compliance in our trial, we instructed patients to mark off each day on a calendar that indicated how many capsules they were to take. Patients were instructed to take the drug at 8 a.m. so we could check plasma levels. We also counted pills. All patients lost their hair, which is hard to do without taking medication.