Cancer Chemother Pharmacol (1994) 34 (Suppl): S 96–S 100

Cancer Chemotherapy and Pharmacology

Etoposide in the treatment of elderly/poor-prognosis patients with small-cell lung cancer

Desmond N. Carney, Anthony Byrne

Mater Misericordiae Hospital, Eccles Street, Dublin 7, Ireland

Abstract. Survival rates for cancer have improved in recent decades, specifically for younger patients. However for those over 65, who account for over half of all cancer patients, mortality rates remain poor. In those with small-cell lung cancer the achievement of cure is possible in only a minority (5–10%). For the elderly and those with extensive disease we have found that the use of oral etoposide offers similar survival rates to more intensive regimens, with minimal side effects and hospitalisation. Thus the expansion of the elderly population mandates for more specific chemotherapeutic approaches in this group.

Key words: Etoposide – Poor prognosis – Elderly patients – Small-cell cancer

Introduction

In the two decades following the declaration of the war on cancer by President Richard Nixon the publication of overall survival figures and mortality from cancer created dismay among the medical and lay communities. The results presented showed an increasing number of people dying from cancer and an overall 5-year survival rate that had essentially remained unchanged, ranging from 49% to 51%. The initial analysis of these results suggested that the efforts put into the management of cancer patients, including pathological evaluation, staging procedures and the evaluation of surgery, radiation therapy and systemic chemotherapy used alone or in combination in the treatment of cancers, had yielded little success. However, detailed analysis of the results generated over that period showed a different picture, namely:

1. There has been a significant improvement in the overall survival and decrease in mortality from cancer among persons younger than 65 years of age.
2. A significant overall cure rate had been achieved for many previously incurable cancers, including lymphomas, Hodgkin's disease, acute leukaemias, testicular cancer and primary bone tumours, results unheard of in the early 1970s.
3. It was clear that two major factors accounted for the increased overall mortality observed. These two factors were the dramatic increase in the number of people dying from lung cancer and the recognition that as the population became a more elderly one, the number of persons developing cancer and subsequently dying from it was increasing dramatically. If the two latter factors, but in particular the increase in the number of in deaths from lung cancer, a disease directly associated with cigarette smoking, were eliminated, then it became clear that a significant impact had been made into the treatment, management and improvement in survival of patients with a range of different cancers.

Lung cancer remains the number one cancer killer in the United States and in the European Community. This year it is estimated that in the United States of America more than 170,000 new cases will be diagnosed and that almost all of these patients will eventually die of their disease, with the overall 5-year survival rate remaining at 5%–7%. Unfortunately, there has been little impact in improvements in the overall survival from lung cancer. For patients with non-small-cell lung cancer (NSCLC) the hope for survival rests on the surgical resectability of the tumour. Systemic chemotherapy with/without radiation therapy has made few inroads into improving the survival of patients with this subtype of lung cancer.

For patients with small-cell lung cancer (SCLC), which accounts for 25% of all new cases of lung cancer, the hope for survival rests in its sensitivity to systemic chemotherapy with/without chest radiation. In many trials it has been demonstrated that among all SCLC patients treated, ap-

Paper presented at the Topoisomerase Inhibitors Conference, University of Maryland Cancer Center, 27–30 October 1993, Monterey, California, USA. Supported in part by Bristol Myers Oncology Division

Correspondence to: D. N. Carney

proximately 80% will obtain a significant remission (complete or partial) with systemic chemotherapy and between 5% and 10% of all patients will be cured of their disease. Indeed, in recent years it has been recognized that among those patients who present with a good performance status and limited-stage (LD) disease, and who are less than 65 years of age, the use of combined modality therapy (i.e. chemotherapy in combination with chest radiation therapy) leads to a significant overall rate of response and a long-term survival rate ranging from 25%–40%. The latter, very optimistic figures would suggest that we are beginning to make a major impact on the survival of patients with LD disease. Unfortunately, only a minority of newly diagnosed patients with SCLC are candidates for intensive combination therapy. For most patients there is a need to design therapeutic strategies that offer them hope of a significant response to therapy and a significant improvement in survival with a meaningful quality of life.

In this paper we discuss our approach to the management of patients with SCLC who at the time of presentation are not candidates for combined modality therapy. These include those patients who are elderly (65 years of age or older), those with disseminated or extensive disease, and those with a poor performance status (PS >2).

Cancer in the elderly

Cancer is a leading cause of disease and mortality in the elderly [1, 2]. Currently in the United States, more than 60% of all deaths due to cancer occur in patients who are older than 65 years. In addition, in the United States it is estimated that 11%–12% of people older than 70 years have a past history of cancer. In the European Community, of the more than 1 million cases of cancer diagnosed each year, 55% occur in those older than 65 years. For certain cancers, including colorectal and prostatic cancer, this figure exceeds 65%.

In 1980 in the United States, 25.2 million people were 65 years of age or older [3, 4]. It is now estimated that by the year 2020 this figure will have more than doubled to an expected 52 million, or 17% of the total population. As the elderly population increases, the number of elderly persons with cancer will also rise significantly. In the years ahead, for the oncology community the development of specific therapeutic strategies for the elderly is required.

The chance of developing cancer rises significantly with age [1, 3]. For people aged 25 years the chances of developing cancer are 1:750. At the age of 65 years this probability is 1:14. Thus, in the United States, people younger than 65 years have an overall cancer incidence of 190:100,000 persons, whereas for those older than 65 years this rate is almost 10-fold higher at 1,983.3:100.000 persons. It is therefore clear that as the number of elderly persons increase the number of deaths from cancers of all types will rise significantly, with predicted increases being approximately 20% for men and 10% for women.

Compounding these problems with cancer in the elderly, it is also recognized that cancer deaths in the elderly are higher among the socio-economically disadvantaged. Almost one-third of all elderly Americans live alone and approximately 30% have no children. The lack of family support compounds the medical care of elderly patients with cancer.

Many factors may contribute to the increased incidence of cancer in the elderly. These include prolonged carcinogenic exposure, e.g. prolonged cigarette smoking, genetic instability and impaired DNA repair as part of the aging process, and alteration or decreased efficiency of immune surveillance. It is likely that the increased incidence of cancer in the elderly is multi-factorial. Nevertheless, in spite of the increased incidence there are factors that contribute to the poor survival of elderly patients who develop cancer, irrespective of the histological subtype. These factors include (1) the failure to recognize early signs and symptoms of cancers and rather to ascribe them to the aging process, (2) the failure to investigate aggressively elderly persons for cancers who present with subtle signs and symptoms, (3) the lack of screening programmes for the elderly, and (4) the prevailing attitudes among many health care workers that cancer in the elderly "is not worth treating" and thus not worth diagnosing. All of these factors contribute to the delay in the diagnosis of cancer in the elderly at an early stage, when better therapeutic results and, indeed, less aggressive treatment might be obtained.

Among elderly patients who are diagnosed with cancer, many other factors may contribute to their poor results. In particular these include the co-existence of other major medical problems that might preclude the use of surgery, radiation or systemic chemotherapy where appropriate, e.g. congestive cardiac failure. In addition, the poor performance status of many patients and, again, the prevailing attitude among health care workers that for elderly patients the treatment, in particular with systemic chemotherapy, is worse than the disease, mitigate against the successful outcome of care of these patients once their disease has been diagnosed.

It is clear that cancer in the elderly is the most rapidly growing area in oncology, and as we head towards the year 2000 we should develop strategies for screening, early detection and treatment of these persons. A decrease in mortality from cancer in the elderly would have a major impact on reducing deaths from cancer in the community as a whole. Specific efforts should be made to study the biological behaviour of cancer in the elderly, to better understand the pharmacology of chemotherapeutic agents in this group, and to better understand the relationships of cancer with other medical problems. In addition, the education of primary care physicians towards a better understanding of the signs and symptoms of cancer in this age group such that an early diagnosis could be achieved would also be of major benefit. Concomitant with this, attempts should be made to alter the general public's attitude to cancer in the elderly such that the aggressive approaches that we take in the younger age group, including prevention and screening, might be designed specifically for the elderly.

Lung cancer in the elderly

Lung cancer remains a major medical issue worldwide and, with few exceptions, the number of new cases diagnosed

each year continue to rise in each country. Unfortunately, as results have remained static overall in the last two decades the mortality from this disease continues to increase with the increasing numbers of cases being diagnosed. Lung cancer occurs with increased frequency up to the age of 70 years; more than 40% of all deaths due to lung cancer occur in the elderly, and this figure appears to be increasing. Between 1973 and 1987 in the United States, when a 15% increase in lung cancer deaths was noted in persons younger than 65 years, there was a 54% rise in lung cancer deaths in the elderly [1].

Biologically, little difference appears to be seen in lung cancer between the younger and the elderly person [5]. Although the same histological subtypes are observed in both age groups, among elderly persons there appears to be a higher number of cases of squamous-cell carcinoma, accounting for approximately 40% of all new cases. As squamous-cell carcinoma tends to be more localized at diagnosis, the increased incidence of this histological subtype may account for the reported decreased frequency of metastatic lung cancer in the elderly, However, the less aggressive approach to staging elderly patients may also explain these differences.

Treatment options for elderly patients with NSCLC are similar to those for younger patients, taking into consideration their performance status and the co-existence of other major medical problems. For such patients, only complete surgical resection offers meaningful hope for long-term survival. For patients with unresectable disease, palliation of symptoms with the goal of an improved quality of life should be the treatment strategy. Until it has been proven to be more effective in other age groups and outside of clinical trials, the use of systemic chemotherapy should not be considered standard among any elderly patients with NSCLC.

SCLC in the elderly

SCLC accounts for 25% of all newly diagnosed cases of lung cancer and is observed in all age groups. Over the past two decades, considerable progress has been made in understanding both the biological behaviour of this disease and the importance of staging procedures in defining the extent of disease for both therapeutic purposes and in predicting prognosis. The use of systemic chemotherapy either alone or in combination with chest radiation therapy has had a major impact in improving the overall survival of patients with this disease [6]. The median survival for untreated patients remains between 6 and 12 weeks, results comparable with those obtained in untreated cases of acute myelogenous leukaemia.

Using systemic treatment with chemotherapy a median survival of 10–11 months is obtained for all patients. Major prognostic factors identified include the age of the patient at diagnosis; the stage of the disease (limited versus extensive); the performance status of the patient; and the presence of metastatic disease in certain sites, including the liver and brain. With systemic chemotherapy approximately 5% of all patients will be cured of their disease.

In recent years many attempts have been made in improving the overall response rate and, more importantly, the overall survival for patients with SCLC. Studies including the use of alternating chemotherapy, high-dose chemotherapy and high-dose chemotherapy with autologous bone marrow transplantation have not demonstrated any significant benefit over the use of standard systemic chemotherapy used in appropriate doses [6]. The more intensive approach, however, has led to significant increases in overall toxicity and to prolonged hospitalization for those patients receiving such treatment, without a major survival benefit. In recent years the most significant advance has been the recognition that for patients who have a good performance status, are younger than 65 years of age and have LD disease the use of combined modality therapy, including systemic chemotherapy with concurrent radiation therapy to the primary chest lesion, now appears to lead to a 2-year disease-free survival approaching 50%, and many of these patients may be cured of their disease. However, the studies evaluating this approach include small numbers of patients, and whether such results can be extrapolated to the community at large needs further evaluation.

Unfortunately, many patients who present with SCLC are not candidates for combined modality therapy. In a survey of consecutive patients who have presented to our unit over a 4-year period, only 26% of more than 300 patients were considered candidates for combined modality therapy. The exclusion criteria for the remainder of the patients included all patients older than 65 years, all patients with extensive-stage disease and all patients with a poor Eastern Cooperative Oncology Group performance status (ECOG PS 3/4). Thus, unfortunately, among all newly diagnosed patients with SCLC, almost 75% are unfit for an aggressive combined-modality approach that might impact significantly on their overall survival.

Among newly diagnosed patients with SCLC, 25% are elderly. The evaluation of many studies would suggest that members of such an elderly population do not benefit in the same significant manner as do younger patients when treated with combined modality or combination chemotherapy alone (Table 1) [7]. Many reasons may account for the poor and variable response observed. In the elderly, concomitant illnesses, delayed diagnosis, the lack of treatment offered or a compromise of drug schedules given are important factors that may impinge upon the survival rate. It is also possible that biological factors inherent within the tumour cells themselves, including the expression of oncogenes and drug-resistant genes, may also be important. In addition, in studies where elderly patients have been treated similarly to the younger age groups with

Table 1. Oral etoposide in SCLC patients (*OR%* Percentage of objective response, *CR* complete response, *MS* median survival)

Patients	*n*	OR%	CR	MS (weeks)
Elderly patients[a]	63	76	20	38
Poor-prognosis patients[b]	70	79	28	40

[a] Oral etoposide alone
[b] Oral etoposide plus carboplatin

intensive multi-drug regimens, they have significantly increased toxicity in addition to a higher induction mortality rates. Moreover, as treatment regimens and schedules have become more aggressive and intensive in recent years, these toxicities have also increased in this age group. Due to the recognition that among all groups of patients with SCLC the treatment applied, whether involving an intensive combined modality or the use of alternating schedules or combination therapeutic schedules alone, gives comparable results, much effort is now being made to identify treatment schedules that will achieve similar results without impinging on the overall survival or the quality of life of all patients with lung cancer. Thus, in recent years we have evaluated the role of etoposide used as a single agent and in combination in the treatment of elderly and unfit patients with SCLC.

Etoposide

Etoposide is among the most active chemotherapeutic agents in SCLC. Indeed, in recent years the combination of etoposide and cisplatin has been considered by many to be the "standard" combination chemotherapy regimen for the treatment of this disease. In the treatment of patients with SCLC, etoposide has been given both in many different schedules and by different routes (i.v. or oral). Of major importance (and as discussed elsewhere in this monograph) is the demonstration of the absolute schedule dependency of etoposide. In patients with SCLC, studies by Slevin et al. [8], who evaluated etoposide as a single agent (day 1 versus days 1–5), and by Abratt et al. [9], who evaluated etoposide (day 1 or days 1–5) in combination with other agents, clearly demonstrated a significantly greater response rate and survival for patients receiving etoposide over 5 days than for patients receiving the same total dose over 24 h.

Further studies using both i.v. and oral preparations of etoposide have evaluated more prolonged dosing of this agent beyond 5 days for up to 21 days. Although such prolonged schedules clearly demonstrated the activity of etoposide in a range of cancers, including some where chemoresistance to "standard" dosing of etoposide was apparent, no comparative trial has compared more prolonged etoposide administration with that of a 5-day schedule. Moreover, it appears that with prolonged scheduling, both toxicity, in particular myelosuppression, and treatment delays are more common.

Oral etoposide has a bioavailability of approximately 50% (range, 15%–70%). Thus, the usual oral dose is twice the i.v. dose [10, 11]. Moreover, a comparison of the pharmacokinectics of oral and i.v. etoposide has revealed few major differences in the distribution, metabolism and excretion of the agent. The availability of oral etoposide has allowed us to carry out a variety of studies in SCLC patients.

Single-agent oral etoposide in elderly patients with SCLC

Elderly patients with SCLC account for 25% of all new cases of SCLC (or approximately 8,000 cases per annum in the United States). These patients are generally unfit candidates for intensive combination chemotherapy or combined modality therapy. For these reasons we selected elderly patients with SCLC to evaluate the efficacy of single-agent oral etoposide given at a daily dose of 200 mg for 5 consecutive days every 3–4 weeks for a total of six cycles of chemotherapy [12]. Concurrent local-field radiotherapy was not used as part of the initial treatment programme. In addition to evaluating efficacy, further goals of this study were to maintain patient treatment on an out-patient basis with minimal hospitalization and to attempt to minimize treatment toxicities without affecting the therapeutic outcome. Pretreatment staging procedures were kept to a minimum.

Among the 63 patients treated (median age, 72 years) an overall response rate of 76% was observed, with 20% of patients achieving a complete clinical and radiological remission. Among patients with LD, 30% achieved a complete response. The median survival was 38 weeks (range, 4–200 weeks), with 10% of the patients being alive and disease-free at 2 years. Currently, three patients remain disease-free at more than 4 years from the onset of therapy. Among all patients the treatment was acceptable, with no patient refusing further therapy. Total alopecia was observed in all cases, and minimal nausea was noted in some patients. There was no treatment-related death, and grade IV myelosuppression was noted in only three patients throughout all courses of therapy (Table 2).

These results in such a high-risk, poor-prognosis group of patients are similar to what is achieved with more intensive and more toxic combination schedules. Indeed, for these 63 patients the average duration of hospital stay was 2.5 days throughout their treatment plan as compared with the total of 35 days observed for patients receiving combination/alternating chemotherapy. In addition, for patients who achieved a complete response with initial oral etoposide and had a disease-free interval of greater than 3 months, the likelihood of a further significant response to oral etoposide in the same schedule was 50%.

More recently we have studied the combination of etoposide (in the same 5-day schedule) with carboplatin given at 300 mg/m^2 on day 1 every 28 days for six cycles in an extended poor-prognosis group of patients with SCLC. In this study, the patients included had to fulfill one or more of

Table 2. Impact of intensive combination chemotherapy in "elderly" patients with SCLC[a]

Time	Age range (years)	Patients (*n*)	Median survival (weeks)	Early death	2-Year survival
1981–1987	56–60	166	44	11%	12%
	66–70	200	30	22%	8%

[a] From Osterlind et al. [5]

the following criteria: (1) an age of ≥65 years (elderly patients); (2) patients with extensive-stage disease, irrespective of age; and (3) patients with an ECOG performance status of ≥3, irrespective of age. Thus far, 70 patients have been evaluable. The median age of these patients was 61 years (range, 29–78 years). Following staging, 21 of the 70 patients had LD. An overall response rate of 79% (58/70 patients) with a complete response rate of 28% (20/70 patients) was observed. The median survival of all 70 patients has been 40 weeks. During the initial cycle of chemotherapy, two patients died of significant myelosuppression. In all others toxicity was acceptable. Among such a poor-prognosis group of patients, these results are similar to, if not better than, what has previously been reported for more intensive schedules.

Discussion

It might be suggested that the use of single-agent chemotherapy in the current treatment of patients with SCLC would be considered unacceptable. This suggestion is based on our belief that combination chemotherapy or more intensive chemotherapy (e.g., high-dose chemotherapy with autologous bone marrow transplantation) has been proven to be the standard treatment for patients with SCLC.

Unfortunately, evaluation of numerous trials over the past two decades has not shown a significant advantage in terms of survival for patients receiving more intensive schedules of chemotherapy [13]. It is true that a modest dose-response relationship does exist, but above a certain standard dose no further clinical benefit ensues. In contrast, however, with increasing dose intensity, more toxicity, including life-threatening toxicity, is observed.

The major advance in the recent care of SCLC has been the recognition that the use of combined modality treatment in good-performance-status patients younger than 65 years of age with LD can achieve a long-term survival (cure?) approaching 50%. For all other patients in poor-prognosis groups, no major advance has been made in the comparison of many different schedules of treatment. Moreover, almost none of these patients will be cured of their disease.

Thus, it seems reasonable that for the foreseeable future our treatment approach for SCLC patients should be based on their placement into two categories:

1. For patients younger than 65 years of age with LD and a good performance status, it appears that combination chemotherapy and chest radiation therapy offer a realistic hope of cure and should be offered to all such patients.

2. For all other patients (>65 years of age, poor performance status and/or extensive-stage disease) managed with current treatment strategies the chance of cure is remote, and the expected median survival is 7–9 months. In such patients we believe that single-agent etoposide or etoposide with carboplatin offer a realistic hope of remission along with an improved quality of life, prolongation of survival, little hospitalization and acceptable toxicity. This approach might also be the start of improving or evaluating new chemotherapy regimens for the treatment of such a poor-prognosis group of patients.

Our results are in keeping with those achieved by other investigators using single-agent etoposide in this disease. In the study by Johnson [14], of 140 patients treated with either etoposide or combination regimens containing Adriamycin, no significant benefit for the combination was observed. In a further study of patients with extensive-stage disease (i.e. high-risk patients), Ettinger [15] failed to demonstrate a benefit for combination chemotherapy over single-agent ifosfamide or single-agent teniposide.

In conclusion, these studies and others have clearly demonstrated the activity and efficacy of single-agent etoposide given orally over at least 5 days to be high in high-risk, poor-prognosis patients with SCLC. In such patients the advantages of oral etoposide include the ease of administration, acceptable toxicity and excellent compliance. The question as to whether more prolonged schedules would be more beneficial needs to be addressed in comparative trials. In addition, these data suggest that these poor-risk, newly diagnosed patients with SCLC, for whom the probability of cure is remote, might also be considered as candidates for inclusion in phase II trials. The use of untreated patients might greatly enhance our ability to identify new active agents for the treatment of patients with this and other diseases.

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