Original Study

Third-Line Chemotherapy in Small-Cell Lung Cancer: An International Analysis

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Abstract

The benefit of third-line chemotherapy for small-cell lung cancer (SCLC) is largely unknown. We reviewed 120 patient records to identify response rates and survival after third-line therapy. The overall response rate and survival benefit were generally modest, however, response in the second-line and normal baseline lactate dehydrogenase (LDH) levels might predict for better outcomes after third-line treatment.

Introduction: Small-cell lung cancer is an aggressive disease for which the mainstay of treatment is chemotherapy. Despite good initial responses most patients will relapse. Some will receive second-line therapy with clinical benefit, but for third-line chemotherapy there is little evidence to guide treatment decisions and the benefits of treatment are unknown. This study investigated the treatment of SCLC in the third-line setting. **Patients and Methods:** An international, multicenter retrospective analysis of patients who received at least 3 lines of chemotherapy for their SCLC was performed. **Results:** From 2000 to 2010, 120 patients were identified from 5 centers: median age 61, 40% (n = 72) limited stage, and 79% (n = 95) Eastern Cooperative Oncology Group performance status of 0 to 1. Only 22% of these patients received 3 distinct lines of chemotherapy. The remainder were rechallenged with a chemotherapy regimen used at least once previously. Six percent received platinum-based chemotherapy in all 3 lines. In third-line, response rate was 18% and median overall survival was 4.7 months. Factors associated with longer survival included normal baseline LDH levels and response to second-line chemotherapy. On multivariate analysis only normal baseline LDH retained statistical significance. Thirty-five patients went on to receive chemotherapy beyond the third line. **Conclusion:** Few SCLC patients receive 3 chemotherapy lines. Most patients were rechallenged with a similar regimen at least once. Response and survival in the third-line setting are modest. Lack of response to second-line chemotherapy and elevated baseline LDH level might predict lack of benefit from third-line treatment. This data set does not include patients receiving fewer lines for comparison.

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Introduction

Small-cell lung cancer (SCLC) is an aggressive malignancy with a propensity for rapid growth, early metastatic dissemination, and acquired drug resistance.[1] SCLC represents 10% to 15% of all diagnoses of lung cancer and is almost always related to cigarette smoking.[2-4] Chemotherapy is the cornerstone of treatment for this disease.[5] Despite being initially exquisitely sensitive to chemotherapy and radiotherapy, most patients subsequently relapse and therefore cure rates remain low.[6]

Small-cell lung cancer is predominately staged, using the Veteran Affairs Lung Study Group (VALSG) staging system, into either limited stage (LS) or extensive stage (ES) disease.[7] Considering its

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aggressive nature and early propensity for distant spread, almost two-thirds of SCLC patients have ES disease at presentation.[8] Clinical stage at presentation still remains the most important prognostic factor for SCLC. ES disease is not curable and patients are treated with palliative intent, with a median survival of 7 to 11 months and less than 5% being alive at 2 years.[9] In contrast, LS disease is potentially curable with aggressive multimodality therapy consisting of concurrent chemoradiotherapy, prophylactic cranial irradiation, and in very rare circumstances, surgery.[10-15] Despite best management, contemporary 5-year overall survival (OS) in LS SCLC is still only 15% to 25%.[9]

Standard first-line chemotherapy in LS and ES SCLC typically consists of a platinum-containing drug such as cisplatin or carboplatin in combination with etoposide (EP). EP replaced the previous regimen of cyclophosphamide, doxorubicin, and vincristine (CAV) as the first-line regimen of choice because it demonstrated longer overall survival (OS) in LS (with a statistically nonsignificant trend for ES disease) and a better toxicity profile in head to head comparisons with CAV.[16-19] Nonetheless, CAV remains a viable alternative in the first-line setting if there is a contraindication to EP and is still used extensively in subsequent lines of therapy.

Most treated patients will relapse, and many will be eligible for second-line therapy. Selection of second-line chemotherapy depends on response to first-line chemotherapy and whether the disease is considered sensitive, resistant, or refractory.[20] Sensitive disease is disease that responded to first-line chemotherapy with duration of response $>$ 3 months, resistant disease is disease that responded to first-line chemotherapy with duration of response of $<$ 3 months, and refractory disease is disease that did not respond or progressed on initial first-line treatment.[21,22] This distinction is important because patients with sensitive disease have a much greater likelihood of responding to further systemic treatment than refractory patients in which the likelihood of response to further systemic therapy is small.[20,23,24]

Patients with refractory and resistant disease are generally treated with a different chemotherapy regimen in the second-line setting.[25,26] Because most patients are treated with EP in the first-line setting, second-line treatment in refractory or resistant disease usually is with CAV or topotecan. Topotecan is approved for use in the second-line setting because it has demonstrated efficacy similar to CAV with better tolerability.[26-28] Considering the greater likelihood of response, patients with sensitive disease are often rechallenged with the regimen they were treated with in the first line setting.[23,29] The guidelines regarding rechallenging are mixed. For example, the National Comprehensive Cancer Network does not recommend this approach, and it is given as a reasonable option in the Cancer Care Ontario lung cancer evidence-based series practice guideline.[30,31]

Patients who respond to second-line treatment, however, will invariably progress and at such time, a decision will need to be made about further therapy. There is a paucity of high quality evidence to guide treatment decisions for SCLC in the third-line setting and no drug or combination regimen is approved in this circumstance. The data on the efficacy of chemotherapy in the third-line setting are sparse and limited to small single-institution retrospective reviews or small single-arm trials.[32-35] Whether third-line treatment is superior to best supportive care is unknown. Considering this paucity of third-line data, we conducted a multinational, large institution, contemporary retrospective review to better quantify and understand the outcomes of patients with SCLC who go on to receive at least 3 lines of systemic chemotherapy.

Patients and Methods

Participating Centers and Patient Selection

Five large cancer centers, 3 from Canada and 1 each from the United Kingdom and Australia participated in this study. All centers obtained local research ethics board approval before initiating data collection. Patients who received at least 3 lines of chemotherapy for SCLC between January 1, 2000 and December 31, 2010 were identified at each center using institutional tumor registries. All patients who received at least 3 lines of chemotherapy during this time period were included in the study. Mixed histology (eg, SCLC and non−SCLC-containing tumors) or other neuroendocrine tumors of the lung (eg, large-cell neuroendocrine lung cancer) were excluded. The third line of chemotherapy was defined as chemotherapy received after progression or failure of 2 other courses of systemic therapy. Rechallenges with the same or similar chemotherapy after completion of a planned course of treatment were considered a subsequent line of treatment. However, changes within a course of therapy (eg, substituting carboplatin for cisplatin) were not considered a new line. As such, patients did not have to receive 3 different chemotherapy regimens to be considered eligible.

Data Collection

Baseline characteristics and known SCLC prognostic factors at diagnosis were recorded. These included: age, sex, disease stage, Eastern Cooperative Oncology Group (ECOG) performance status (PS), serum lactate dehydrogenase (LDH), serum sodium, and hemoglobin.[36] Disease stage was recorded as LS or ES using the VALSG staging system. The type of first-, second-, and third-line chemotherapy regimens administered, number of cycles, date of administration, and tumor response for each line of therapy were also documented. Chemotherapy regimens were classified into 4 categories: platinum-based, CAV-based, topotecan-based, and other. The platinum-based category included regimens that used cisplatin or carboplatin.

Outcomes

Primary study outcomes were response rate (RR) and median OS to third-line chemotherapy. The secondary outcome was progression-free survival (PFS). Best response to each line of therapy was assessed by the site-specific investigator using the Response Evaluation Criteria in Solid Tumors version 1.1.[37] Patients with a complete response or partial response were responders and those with stable disease or progression of disease were nonresponders. Tumor assessment intervals were institution-specific and there was no central imaging review. PFS was defined as the time from initiation of chemotherapy to the time of documented progression. In cases in which clinical examination documented progression before imaging confirmation, the date of clinical progression was used as the definitive date of progression. In all other circumstances, radiologic progression was used as the definitive date of progression. OS was defined as the time from the start of third-line treatment until time of death or last known follow-up.