Gemcitabine and Cisplatin Combination in Early-Stage Non-Small-Cell Lung Cancer

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A number of randomized clinical trials now support the conclusion that the combined-modality regimen that includes gemcitabine (Gemzar) and cisplatin (Platinol) may improve survival in disseminated non-small-cell lung cancer.

Introduction

In non-small-cell lung cancer surgical resection is possible in only 20% to 30% of all cases, mainly because of locally advanced disease and high incidence of distant metastases. For early-stage resectable non-small-cell lung cancer, 5-year survival is 60% for stage I, 40% for stage II, and 20% for limited stage IIIA; in case of mediastinoscopy positive N2 disease, 5-year survival drops to 5% to 10%. According to historical series, the 5-year survival is 0% in unresectable, locally advanced, bulky stage IIIA or IIIB disease. The overall 5-year survival across all stages of non-small-cell lung cancer ranges between 8% and 12% both in Europe and the United States, mainly because of early dissemination of disease, which precludes the possibility of any locoregional treatment (surgery or radiation therapy). Therefore, it seems quite clear that the overwhelming majority of non-small-cell lung cancer patients requires an effective systemic treatment to improve these dismal survival figures.

A meta-analysis, conducted in 1995, of all randomized trials focusing on the role of chemotherapy in non-small-cell lung cancer showed a small but significant survival benefit in favor of cisplatin-based systemic chemotherapy across all stages. The results of this meta-analysis have stimulated the use of chemotherapy in addition to locoregional treatment in the management of locally advanced non-small-cell lung cancer.

In the past 15 years, preoperative or neoadjuvant chemotherapy has been widely employed in the treatment of stage IIIA disease in many phase II trials and in some small phase III randomized studies.

Preoperative phase II chemotherapy studies, as exemplified by the Memorial Sloan-Kettering and Toronto experiences with the MVP regimen (mitomycin [Mutamycin], vinblastine, cisplatin) have shown improved survival compared with historical controls, with median survival of 15.5 to 19 months and 5-year survival consistently around 18% vs 9% for historical controls.

These favorable results have been validated by three small, randomized trials which seem to indicate that neoadjuvant therapy in stage IIIA improves survival. Unfortunately, the results cannot be considered conclusive because of the premature interruption of these studies on the basis of interim analysis data and a possible worse selection of patients in the control arm which consisted of surgery alone. In the Pass et al trial (27 stage IIIA N2 patients), both median survival (28.7 months vs 15.5 months) and disease-free survival (12.7 months vs 5.8 months) seem to favor the neoadjuvant chemotherapy arm, but statistical significance was not reached.

Two subsequent studies from M. D. Anderson Cancer Center and the Spanish Lung Cancer Group showed a statistically significant improvement in survival for those patients who received preoperative chemotherapy vs surgery alone. The design of these trials was very similar: induction chemotherapy consisted of cyclophosphamide (Cytoxan, Neosar), etoposide, and cisplatin in the M. D. Anderson experience, and mitomycin, ifosfamide (Ifex), and cisplatin in the Spanish study. The survival advantage conferred by induction chemotherapy was maintained after 3 and 5 years of follow-up.
New Agents in Neoadjuvant Chemotherapy

Until the early 1990s, the regimens used in phase II/III studies as induction chemotherapy always consisted of the double or triple combinations of cisplatin with old active drugs such as etoposide, mitomycin, vinca alkaloids, and ifosfamide. During the 1990s, a number of new drugs with different mechanisms of action showed important activity as single agents in non-small-cell lung cancer: the nucleoside analog gemcitabine; the microtubulin inhibitors paclitaxel, docetaxel (Taxotere), and vinorelbine (Navelbine); and the topoisomerase I inhibitors irinotecan (CPT-11, Camptosar) and topotecan (Hycamtin) showed response rates greater than 20%. In patients with metastatic non-small-cell lung cancer, these new agents in combination with a platinum compound (either cisplatin or carboplatin [Paraplatin]) have demonstrated superior response rates and/or survival compared with cisplatin alone or older platinum-based combinations.[9]

In particular, gemcitabine and cisplatin in combination have revealed a strong synergism in preclinical models.[10] In three different large randomized trials of advanced non-small-cell lung cancer, this new regimen has shown a survival advantage vs cisplatin alone [11] and higher response rates than etoisode/cisplatin[12] and the mitomycin/ifosfamide/cisplatin combination.[13] On the basis of this activity in advanced disease, this regimen has been tested in several phase II studies in the more favorable stage III non-small-cell lung cancer as induction chemotherapy to surgery or radiotherapy.

In 1996, the EORTC initiated a phase II trial to define the toxicity and activity of this new regimen as an induction treatment for patients with stage III N2 non-small-cell lung cancer, within a large ongoing randomized trial comparing surgery with radiotherapy after neoadjuvant chemotherapy.[14] Forty-seven patients received gemcitabine 1,000 mg/m^2 on days 1 through 8 and 15 and cisplatin 100 mg/m^2 on day 2, every 4 weeks. Of the 47 eligible patients, 33 had objective responses (70.2%, 95% confidence interval [CI] = 55.1%-82.7%) with three complete and 30 partial responses. Resections were considered complete in 71% of these patients who underwent thoracotomy. Median survival was 18.9 months, and 1-year survival was 69%. Grade 3/4 thrombocytopenia occurred in 60% of patients without any episodes of bleeding and caused withholding of gemcitabine on day 15 in 48% of the courses.

Similar results have been reported in a series of small phase II studies of gemcitabine and cisplatin as induction chemotherapy in stage III non-small-cell lung cancer. In 1996, we started an Italian prospective phase II trial to evaluate the safety and activity profile of a new, 3-week schedule of gemcitabine and cisplatin as induction chemotherapy to surgery or radiotherapy in stage IIIA/IIIB non-small-cell lung cancer. A total of 110 patients were treated with gemcitabine 1,250 mg/m^2 on days 1-8 and cisplatin 80 mg/m^2 on day 2. Ninety males and 20 females were enrolled. The median age was 61 years (range: 39-79) and all patients had 0 or 1 ECOG performance status (49 and 61, respectively). Fifty-five patients had squamous carcinoma, 37 adenocarcinoma, 6 large cell carcinoma; and 12 unknown non-small-cell lung cancer. A median number of four courses (range: 2-8) was given. Response assessment showed 69 partial responses (62%) and 3 pathologically confirmed complete responses (3%); 34 patients (31%) remained with stable disease and only 4 experienced progression; 31 patients (28%) underwent thoracotomy and were completely resected.

Treatment was well tolerated. Twenty-two patients experienced World Health Organization (WHO) grade III neutropenia and 3 developed grade IV neutropenia. WHO grade III and IV thrombocytopenia was recorded in 22 and 12 patients, respectively. No toxic deaths were observed.[15]

Neoadjuvant Chemotherapy in Early Stages of Non-Small-Cell Lung Cancer

In these studies, the activity of the gemcitabine/cisplatin combination in stage III non-small-cell lung cancer is among the highest and compares very favorably with the results of published phase II and III studies.

Response rates were in the range of 60% to 70%. Surgical resection and pathologic downstaging of mediastinal lymph nodes occurred in more than 50% of patients, despite significant initial tumor...
burden (most patients had bulky N2 unresectable disease at the start of treatment).

These considerations indicated that the gemcitabine/cisplatin combination is a very active induction chemotherapy and prompted Italian investigators to evaluate its role in a more favorable setting, namely stage I/II and selected IIIA resectable cases. Recently, in the United States and Europe, neoadjuvant chemotherapy has been evaluated in early-stage non-small-cell lung cancer, both in phase II and III studies. In a multicenter US phase II trial of 94 patients with T2 N0, T1/2N1; and T3 N0/1 disease, investigators delivered two cycles of carboplatin/paclitaxel followed by surgery and by three additional cycles of chemotherapy.[16] Major responses occurred in 56% of cases; 4% of patients were completely resected.

In a randomized phase III study of 373 patients, Depierre et al assessed the impact of neoadjuvant chemotherapy (two cycles of MIC regimen) followed by surgery vs surgery alone, on survival in stage I/II and II/III non-small-cell lung cancer.[17] In a Cox regression model adjusted for stage, the effect of preoperative chemotherapy was significantly favorable with a relative risk of .77 ($P = .05$). Disease-free survival was significantly longer ($P = .02$) and the risk of distant recurrence was significantly lower ($P = .01$) in the preoperative chemotherapy arm.

After these trials, we designed a randomized study comparing surgery vs induction chemotherapy with gemcitabine/cisplatin followed by surgery in early-stage patients. Overall survival will be the main end point of this trial, which is currently ongoing in Italy.

**New Drugs in Combined-Modality Treatment**

The 1995 meta-analysis showed that chemotherapy improves survival when added to radiotherapy for patients with unresectable stage III non-small-cell lung cancer.[3] These data have been recently confirmed by two consecutive prospective trials from the Cancer and Leukemia Group B (CALGB) and Radiation Therapy Oncology Group (RTOG), both reporting a survival advantage in favor of sequential chemoradiotherapy vs radiotherapy alone.[18,19] Concurrent cisplatin-based chemoradiotherapy vs sequential radiotherapy alone has also been evaluated in phase III trials with promising results: Furuse et al showed that median and long-term survival were clearly superior in the concurrent arm of split-course thoracic radiotherapy and MVP chemotherapy vs the sequential arm of MVP before thoracic radiotherapy.[20]

Recently, new drugs have been evaluated by the CALGB in a randomized phase III study exploring sequential and concurrent chemoradiotherapy in unresectable stage III non-small-cell lung cancer. This study was designed to investigate three new combinations plus cisplatin/radiotherapy combinations: cisplatin/gemcitabine, cisplatin/paclitaxel, and cisplatin/vinorelbine. Each combination was given initially as induction chemotherapy for two cycles and then concurrently with radiotherapy. The results of this study are very promising, with a median survival of 18 months, 1-year survival of 66%, and an acceptable toxicity profile.[21]

**Conclusions**

The new gemcitabine/cisplatin regimen has been extensively evaluated in advanced non-small-cell lung cancer in phase II and phase III randomized trials with a response rate ranging between 21% and 40% and a median survival of approximately 9 months. These data place this combination among the most active regimens in non-small-cell lung cancer and suggest the importance of a thorough evaluation in more favorable disease stages. The ongoing trials in the neoadjuvant setting and in the sequential or concurrent approach with radiotherapy in early non-small-cell lung cancer will contribute to define the role of this regimen in the combined treatment of non-small-cell lung cancer.

**References:**


Links: