Gemcitabine in non-small cell lung cancer: just another drug?

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Lung cancer is the leading cause of cancer death in Mexico and most countries. This highly lethal malignancy remains as a great challenge to oncologists due to its aggressive tumor biology and poor sensitivity to radiation and chemotherapy. In addition, no screening strategies have shown benefit in terms of reducing its mortality. Consequently, most patients present with locally advanced disease no amenable to surgical treatment.

At diagnosis, patients with NSCLC can be divided into 3 groups that reflect the extent of disease and treatment approach. The first group of patients has tumors that are surgically resectable (generally stages I and II). This is the group with the best prognosis, depending on a variety of tumor and host factors. Patients with resectable disease who have medical contraindications to surgery can be considered for curative radiation therapy. The second group includes patients with either locally (T3-T4) or regionally (N2-N3) advanced lung cancer who have a diverse natural history. This group is treated with radiation therapy or, more commonly, with radiation therapy in combination with chemotherapy or other therapy modalities. Selected patients with T3 or N2 disease can be treated effectively with surgical resection alone or in some cases, chemoradiation or neoadjuvant chemotherapy allows for surgical resection with a curative attempt. The final group of patients have distant metastases (M1) found at the time of diagnosis. This group can be treated with radiation therapy or chemotherapy for palliation of symptoms from the primary tumor.

As with many other malignancies, cisplatin is among the single agents one of the most effective drugs with response rates between 30 to 40%. This has established the use of this agent commonly in combination with other drugs. Until recently, chemotherapy was considered to be more successful in the treatment of small cell lung cancer than NSCLC, but this is no longer true. In a recent meta-analysis of randomized trials in NSCLC, cisplatin-based chemotherapy was shown to prolong survival for patients across all stages of the disease. A role for adjuvant cisplatin-based therapy has been shown in early stage disease, and cisplatin-based therapy was shown to improve survival when combined with radiotherapy in locally advanced disease and as a single modality in metastatic disease. Other randomized trials have shown that cisplatin-based therapy improved quality of life in both stage III and IV NSCLC patients and reduced the cost of medical care compared with best supportive care. Cisplatin-based therapy should therefore be considered the standard treatment for all NSCLC patients with locally advanced or metastatic disease.

However, over the last 5 years, new agents have emerged that have increased single-agent response rates, increased survival, and, for the most part, reduced toxicity. Among the most promising of these new drugs is the antimetabolite gemcitabine. Gemcitabine (2',2'-difluorodeoxycytidine) is an antineoplastic agent with activity against a variety of solid tumors. This drug is phosphorylated intracellularly to produce di and triphosphate active forms, which in turn exert their cytotoxic effects, by inhibition of DNA replication and repair. The difluorodeoxycytidine triphosphate competitively inhibits DNA polymerase and terminates DNA chain elongation. The di-phosphate form is a potent inhibitor of ribonucleotide reductase, an action that reduces deoxynucleotide pools. Decreased cellular concentrations of deoxycytidine triphosphate permits more rapid phosphorylation of gemcitabine and reduces the metabolic clearance of gemcitabine nucleotides by deoxycytidine monophosphate deaminase.

Several single-arm gemcitabine Phase II studies involving more than 400 patients show validated res-
ponse rates in more than 20% of the patients. These positive results have also been confirmed in randomized Phase II studies. Gemcitabine’s unique mechanism of action, its lack of overlapping toxicity with other agents, and its favorable toxicity profile also define it as an ideal candidate for combination therapy. Importantly, gemcitabine is highly synergistic with cisplatin and in combination yields response rates from 31 to 54% with a median survival time between 8.4 and 15.4 months and a 1-year survival rate between 30% and 59%. In addition to the clinical research of gemcitabine-cisplatin combinations, gemcitabine has also been tested in various double and triple combinations with carboplatin, paclitaxel, docetaxel, vinorelbine, and ifosfamide. Investigations combining gemcitabine with radiation therapy are on-going, based in vitro and in vivo studies that show the radiosensitizing properties of this antimetabolite.

In this issue of the Revista del Instituto Nacional de Cancerología, Dr. Gallardo’s group present their results of a phase II study of single agent gemcitabine for the treatment of locally advanced lung cancer patients (stages IIIA, IIIB and IV). They show that indeed this antimetabolite as a single agent at a dose of 1000 mg/m²/week in courses of 28 days proved to be effective achieving a response rate of 33% at expenses of negligible toxicity. For this patient population who frequently has comorbid conditions (lung and heart disease), toxicity turns out to be a very important issue. Thus, the overall results of this treatment in terms not only of response but also in progression-free survival (3.5 months) and 1-year survival of 22% is encouraging. These figures are better with lesser toxicity as compared to cisplatin-etoposide combination therapy. The results of this study also underscore the importance of the dose intensity for gemcitabine as the 33% response rate achieved is superior to that obtained with doses below 900 mg/m²/week. Much remains to be explored concerning other schedules of administration for this drug as well as its combination with non-cisplatin containing regimens. Thus, in vitro and in vivo testing for synergistic effects with other drugs and in the near future with novel therapeutic agents (monoclonal antibodies, protein kinase inhibitors, antiangiogenic drugs, etc.) should be an obligatory research avenue.

Progress in the treatment of NSCLC has been slow. Gemcitabine, either alone or in combination with cisplatin or non-cisplatin drugs, undoubtedly is contributing to make current treatment of the lung cancer patients not only more effective but also better tolerated. We should remind that cure is not the only aim of cancer treatments and in patients with advanced lung cancer, to have an effective and well-tolerated drug is a useful tool.

REFERENCES