Third-Line Chemotherapy for Advanced Non-Small-Cell Lung Cancer — Is There Enough Evidence to Support its Use?

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First-line Chemotherapy

Before the introduction of targeted therapy in advanced non-small-cell lung cancer (NSCLC), systemic chemotherapy was the only modality available for patients whose disease status did not allow curative-intent surgery or radiotherapy. Platinum-based combination chemotherapy has become the standard of care for physically fit patients, since publication of a meta-analysis in 1995 and the American Society of Clinical Oncology guidelines in 1997.[1,2] Advances have been made in recent years regarding the selection of first-line chemotherapy regimens. Large-scale, randomized studies have found that different regimens may have little impact on patient survival, as long as a platinum-based compound and a third-generation chemotherapeutic agent (e.g. paclitaxel, docetaxel, vinorelbine, gemcitabine, irinotecan) are included in the 2-drug regimen.[3] For patients with good performance status (Eastern Cooperative Oncology Group [ECOG] score 0 or 1), monotherapy or triple-therapy schedules are not recommended, although monotherapy may be appropriate for patients with poor performance status.

Second-line Chemotherapy

Most patients who receive first-line chemotherapy will eventually progress and face the question of whether second-line chemotherapy should be given. Several large, randomized studies of second-line regimens have been completed. Docetaxel 75 mg/m^2 administered 3 times weekly was superior to best supportive care in terms of overall survival; it was also superior (although not statistically significantly) to docetaxel 100 mg/m^2, vinorelbine or ifosfamide regarding 1-year survival.[4,5] In recent guidelines from the American Society of Clinical Oncology,[6] docetaxel monotherapy was recommended as the second-line treatment for advanced NSCLC patients who had already received chemotherapy. Further, pemetrexed is a novel antimetabolite that has a demonstrable effect as second-line therapy for NSCLC. A recent, randomized study showed that pemetrexed had similar efficacy to docetaxel as a second-line treatment for NSCLC, but with much less treatment-related toxicity, especially hematotoxicity.[7]

Third-line Chemotherapy

With improvements in chemotherapy, more patients survive, after having received at least 2 treatment regimens, than was previously the case. Indeed, gefitinib demonstrated a reasonable response rate and toxicity profile as a third-line treatment in the Iressa® Dose Evaluation for Advanced Lung Cancer (IDEAL)-1 study.[8] Erlotinib was superior to placebo in terms of survival in advanced NSCLC patients who had failed first- or second-line treatment.[9] These novel, targeted treatments against epidermal growth factor receptors were a big breakthrough for heavily pretreated lung-cancer patients. However, not all patients can benefit from these drugs. It is reasonable to offer third-line chemotherapy to patients with good performance status if a specific schedule has demonstrated safety and efficacy in clinical trials. Unfortunately, such trials of third-line schedules are lacking. Only anecdotal reports exist in the literature,

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response rates have generally been low, and survival has not been clearly described.

In this issue of the journal, Chen et al propose a regimen for patients with advanced NSCLC who have already received chemotherapy.[10] Weekly gemcitabine was given to 20 patients as second-line ($n = 3$) or third-line treatment ($n = 17$). Two patients who received gemcitabine as third-line treatment responded, associated toxicities were acceptable, and responses and survival times were similar to those reported for weekly gemcitabine used as second-line treatment. The authors concluded that third-line therapy with weekly gemcitabine is effective, has limited toxicity, and can be considered for patients who require chemotherapy after failure of 1 or 2 previous regimens.

Patients who are able to receive third-line chemotherapy are often exposed to many cycles of toxic drugs, and thus often have damaged bone marrow and nervous systems, and compromised renal and hepatic function. Therefore, only compounds with a wide therapeutic window can be considered, and weekly gemcitabine is one such schedule with low systemic toxicity. In addition, cancer patients always develop resistance to chemotherapeutic agents after long-term exposure, and cross-resistance between chemotherapeutic agents may be important, particularly if a compound with a similar mechanism of action to that of a previous regimen constituent is used in a subsequent treatment schedule. Thus, if gemcitabine has not been used previously, it is probably the best monotherapy choice among the 5 third-generation chemotherapies; indeed, 3 of these chemotherapies (paclitaxel, docetaxel and vinorelbine) share similar mechanisms of action (microtubule inhibition) and resistance (p-glycoprotein over-expression).

Chemotherapy remains the mainstay of treatment for advanced NSCLC in this era of targeted treatment, and clinical oncologists continue to explore any potential treatment advances that can be provided to patients. Consequently, third-line chemotherapy is given to many patients with advanced NSCLC. It is now time to generate evidence to show that third-line chemotherapy is indeed helpful to such patients. Based on anecdotal observations of efficacy for such chemotherapy reported in this issue of the journal,[10] a formal trial of third-line chemotherapy in NSCLC should be designed and conducted. Potential investigators should be encouraged to perform a multicenter trial with the assistance of a cancer group such as the Taiwan Cooperative Oncology Group.

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