Paclitaxel (Taxol) and vinorelbine (Navelbine) are both microtubule toxins but with opposite mechanisms of action. Paclitaxel promotes the assembly of microtubules, whereas vinorelbine prevents microtubule assembly.

Introduction

By combining active agents with different mechanisms of action and/or toxicity to prevent drug resistance, combination chemotherapy can offer better therapeutic results for cancer patients than single-agent treatment. The advantages of combination chemotherapy have been demonstrated in the treatment of Hodgkin’s disease, non-Hodgkin’s lymphoma, breast cancer, testicular carcinoma, and small-cell lung cancer.[1]

Vinorelbine (Navelbine) and paclitaxel (Taxol) affect microtubular functions but act at different binding sites and in different steps of mitosis. Vinorelbine inhibits the formation of microtubules from tubulin dimers, whereas paclitaxel stabilizes and prevents depolymerization of microtubules.[2,3] Adams has demonstrated synergistic cytotoxicity of these two agents against MCF-7 and MDA-MB-231 breast cancer cells in vitro.[4] In addition, Knick et al have demonstrated improved survival with the combination of vinorelbine and paclitaxel vs either agent alone (80% vs 0%, respectively) in treating mice bearing P388 leukemic cells, without increasing toxicities.[5] We have also shown increased cytotoxicity of vinorelbine and paclitaxel against A549 cells (human adenocarcinoma of the lung), as compared with either agent alone.

When used as first-line therapy for advanced non-small-cell lung cancer (NSCLC), vinorelbine alone produces an objective response rate of 14% to 30% and a 1-year survival rate of 25% to 30%.[6,7] When used as a single agent in patients with metastatic non-small-cell lung cancer, paclitaxel is associated with a 21% to 24% objective response rate and a 40% 1-year survival rate.[8,9] These results clearly demonstrate that vinorelbine and paclitaxel are among the most active drugs when used as single agents or in combination chemotherapy regimens for the treatment of non-small-cell lung cancer. Because there is no standard second-line therapy for patients with refractory and/or metastatic non-small-cell lung cancer, who have an urgent need for effective treatment, we chose to study this combination in an in vitro model and in a clinical trial.

In Vitro Studies

In our in vitro studies, A549 cells were cultured in RPMI1640 medium with 10% fetal calf serum in incubator at 37 °C and 5% carbon dioxide. Exponentially growing A549 cells were then treated with various concentrations of vinorelbine and paclitaxel and with different sequences of treatment. The cytotoxicity was evaluated by colony-forming assay. The distribution of cell cycles was analyzed by Coulter flow cytometer, using an EPEC program. We were able to show that at low concentrations of both agents (≤ 10 nM/L), there was a synergistic cytotoxicity against A549 when both drugs were incubated concurrently or when administration of vinorelbine was followed by paclitaxel. However, there was no increase in G2/M blockage in the cell-cycle studies beyond either agent’s activity to block transition of mitosis steps (Table 1).

Clinical Trial

Patients and Methods

To be eligible for our clinical trial of vinorelbine and paclitaxel in non-small-cell lung cancer, patients had to meet the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate hematologic, hepatic, and renal function; measurable disease; failure of one prior
chemotherapy regimen; and no prior exposure to vinca alkaloids or paclitaxel. All patients provided signed informed consent. After 15 patients had been enrolled, the trial was opened to patients who had not received previous chemotherapy. The initial treatment schedule was vinorelbine, 25 mg/m², on days 1 and 8 and paclitaxel, 175 mg/m², intravenously over 3 hours on day 2. The decision to administer paclitaxel after vinorelbine was based on the short half-life of paclitaxel (3 to 6 hours) compared with the long half-life of vinorelbine (22 to 40 hours). This schedule could thereby fulfill the requirement of synergism observed in vitro with either concurrent administration or vinorelbine first followed by paclitaxel. All patients received granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) 5 µg/kg/day subcutaneously from day 3 (except on day 8), until the absolute neutrophil count reached ≥ 10×10⁹/L. Because of myelosuppression, vinorelbine frequently could not be administered on day 8. Therefore, after 11 patients had been enrolled in the trial, the schedule was changed to vinorelbine on days 1 and 2 and paclitaxel on day 2. The treatment was repeated every 3 weeks. The patients were also given oral pyridoxine, 100 mg/day, to prevent and alleviate any symptoms of neuropathy. The survival time was calculated from time of entry until death or the last day the patient was known to be alive. Survival was estimated by the Kaplan-Meier method.[10] Evolution of Chemotherapy

During the 1980s, few new agents were recognized in the treatment of non-small-cell lung cancer. Dose response was studied for cisplatin in a prospective, randomized trial by the SWOG.[14] No advantage was demonstrated by doubling the dosage of cisplatin from 100 to 200 mg/m² or by adding mitomycin to the high-dose cisplatin arm. Because the results of this trial duplicated the SWOG results with other cisplatin-based combinations (ie, a median survival duration of 5.5 to 7.2 months and a 1-year survival rate of 23%), the SWOG retained cisplatin alone at a dosage of 100 mg/m² as its active control arm. Based on a similar experience with cisplatin plus etoposide, the ECOG entered the 1990s with this combination as its active control arm. During the past 5 years, several new agents with activity in non-small-cell lung cancer have been identified (Table 1).

Vinorelbine (Navelbine) [A new antitubulin with a classic mechanism of action, vinorelbine has an improved therapeutic index attributable to a decreased occurrence of neurotoxicity. As a single agent, vinorelbine has produced response rates of 12% to 17%. Its median survival duration, however, is in the range of that observed with cisplatin-based combinations (28 to 32 weeks).[15,16] In a controlled trial, survival was superior with vinorelbine as compared with 5-FU plus leucovorin.[16] Of the single agents that have been tested against other regimens, only one other drug (carboplatin) has demonstrated a survival advantage.[13] A French trial compared vinorelbine alone with the combination of vinorelbine plus cisplatin or the standard European combination of vindesine (Eldisine) plus cisplatin.[17] The new combination showed a statistically significant advantage over the standard combination (median duration of survival, 40 vs 31 weeks; P = .04), with more hematologic toxicity but less neurotoxicity. In a subsequent SWOG study, we compared cisplatin plus vinorelbine to our standard regimen of cisplatin alone.[18] The combination yielded a superior response rate (26% vs 9%) and 1-year survival rate (36% vs 18%; P = .001). Hematologic toxicity with the combination was more severe but within acceptable limits (a 1% mortality rate from neutropenic sepsis and an overall mortality rate of 3%).

Paclitaxel (Taxol) [The taxanes, of which paclitaxel is the first, are a new class of agents that exert their effects by stabilizing the polymerized form of tubulin. Paclitaxel produced a 24% response rate among 48 patients in separate phase II trials,[19,20] and the 1-year survival rate was 35% in the latter ECOG pilot study.[20] In phase II trials, paclitaxel has been combined with cisplatin or carboplatin. The former combination is active but is associated with cumulative neurotoxicity.[21] Both high-dose (250 mg/m²) and low-dose (135 mg/m²) paclitaxel, combined with cisplatin, produced higher response rates when compared with the standard therapy of cisplatin plus etoposide (27% to 32% vs 12%; P < .001).[22] Each paclitaxel arm also produced longer median duration of survival (9.6 to 10 months vs 7.7 months) and higher 1-year survival rates (37% to 39% vs 32%), but the differences were not statistically significant. When the paclitaxel-containing arms were combined, however, there was a statistically significant survival advantage compared with cisplatin plus etoposide (P = .04). The higher dose of paclitaxel produced more severe neurotoxicity and myelosuppression, despite its combination with granulocyte colony-stimulating factor (filgrastim [Neupogen]).
Several abstracts have been presented on the activity of carboplatin plus paclitaxel in phase II trials,[23-25] and one paper was recently published by Langer et al.[26] The overall response rate in these trials was on the order of 50% (range, 25% to 63%), with median survival duration of 38 to 53 weeks. Taken at face value, the combination of these two agents may be the most active available therapy at acceptable levels of toxicity. However, in the study by Langer et al, which found a median survival duration of 53 weeks, 37% of patients had unanticipated hospitalizations during treatment, primarily because of myelosuppression.[26]

Docetaxel (Taxotere) — The other taxane in clinical use, docetaxel, was initially administered at a dosage of 75 to 100 mg/m$^2$ every 3 weeks and without the routine premedication that is required for paclitaxel. It is now appreciated, however, that steroid premedication is useful in the prevention of hypersensitivity reactions to docetaxel. Steroids also delay and ameliorate the development of a second side effect that is peculiar to docetaxel: peripheral edema and third-space fluid accumulation related to cumulative dose.

As a single agent, docetaxel produced a response rate of 31% in initial trials. The activity of this agent in patients with previously treated, platinum-refractory non-small-cell lung cancer is of particular interest: A response rate of 19% has been observed in 72 patients, with a projected survival rate of approximately 40% at 1 year.[27,28] If these observations are validated by other investigators, docetaxel will be the first agent identified as having useful activity in the setting of platinum failure.

Gemcitabine (Gemzar) — Like cytarabine, gemcitabine is a cytidine analog. However, gemcitabine has a very different spectrum of activity in preclinical systems as well as in human cancers, possibly because of its longer intracellular half-life in its form as the triphosphorylated compound. This agent is usually given on a weekly schedule and has been reported to produce response rates in the range of 20% in phase II trials.[29-31]

Gemcitabine produces a mild flu-like syndrome and moderate neutropenia, but it has few other side effects in most patients. This favorable pattern of toxicity has led to its use in a two-drug combination with cisplatin. Three recent abstracts[32-34] reported that this combination yielded response rates of 30% to 44% in stage IV disease, with acceptable toxicity; survival data are not yet mature.

Irinotecan (Camptosar) stabilizes the topoisomerase I "cleavable complex" in a fashion analogous to the effect of etoposide on topoisomerase II. In a study in Japan, irinotecan produced a 33% response rate among 40 patients with stage IV non-small-cell lung cancer, and the median survival duration was 9.2 months.[35] Leukopenia and diarrhea are dose-limiting toxicities and have poor predictability (especially the latter, which can be life-threatening).

In other studies in Japan, irinotecan was combined with cisplatin, with or without vindesine, and yielded response rates approaching 50%.[36,37] In the United States, phase II trials of the combination of cisplatin and irinotecan are nearing completion, with results yet to be reported.

Topotecan (Hycamtin) — Also studied in non-small-cell lung cancer, topotecan has a lower reported response rate than irinotecan but a comparable median survival rate.[38] Topotecan has the advantage of producing fewer problems with diarrhea and bears investigation in combination with other agents.

Conclusions

Cisplatin, alone or in combination, probably affects survival in advanced non-small-cell lung cancer. Carboplatin and vinorelbine have had a beneficial effect on survival when used as single agents in randomized trials. The combination of cisplatin and vinorelbine has shown reproducible effects on survival when compared with standard cisplatin-based therapy; this regimen currently represents a reasonable community standard for the treatment of non-small-cell lung cancer.

Paclitaxel and docetaxel are active new agents. The combination of carboplatin and paclitaxel warrants comparison with other treatments in randomized trials. Paclitaxel is of special interest because of its activity in platinum-refractory disease. Other new agents of interest include gemcitabine and irinotecan, although their roles in combination therapy have yet to be defined.
References:


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