Clinical Update: Oncology Pharmaceuticals

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This clinical update reports on the most recently published, relevant clinical findings demonstrating the potential of targeted oncology pharmaceuticals for increasing the survival rate of cancer patients, as compared with the standard oncological therapeutics relied upon to date. The results of the clinical investigations show therapeutic promise, but these findings must be corroborated with additional studies in other patient populations. Positive findings must be attained before the new combination of drugs can be recommended for standard therapy. In some cases, clinical studies revealed the efficacy and safety of a new pharmaceutical for the treatment of a cancer type refractory to previous treatments. In other instances, the use of known chemotherapeutic drugs at different doses or combinations might increase the survival rate in patients with advanced disease.

LYMPHOMA

The standard treatment for patients with diffuse large-β-cell lymphoma is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Rituximab, a chimeric monoclonal antibody against the CD20 β-cell antigen, has therapeutic activity in diffuse large-β-cell lymphoma. A randomized trial was conducted to compare CHOP chemotherapy plus rituximab with CHOP alone in elderly patients with diffuse large-β-cell lymphoma.1 Previously untreated patients with diffuse large-β-cell lymphoma, 60 to 80 years old, were randomly assigned to receive either eight cycles of CHOP every three weeks (197 patients) or eight cycles of CHOP plus rituximab given on day one of each cycle (202 patients).

The rate of complete response was significantly higher in the group that received CHOP plus rituximab than in the group that received CHOP alone (76% vs. 63%, P=0.005). With a median follow-up of two years, event-free and overall survival times were significantly higher in the CHOP plus rituximab group (P<0.001 and P=0.007, respectively). The addition of rituximab to standard CHOP chemotherapy significantly reduced the risk of treatment failure and death (risk ratios, 0.58 [95% confidence interval, 0.44 to 0.77] and 0.64 [0.45 to 0.89], respectively). Clinically relevant toxicity was not significantly greater with CHOP plus rituximab. It was concluded that the addition of rituximab to the CHOP regimen increases the complete-response rate and prolongs event-free and overall survival in elderly patients with diffuse large-β-cell lymphoma, without a clinically significant increase in toxicity.

The combination regimen is the first to improve survival in this group of patients in more than 20 years. Data from a U.S. trial involving over 600 patients receiving rituximab and CHOP should be available later this year. Dr. Bruce D. Cheson of the National Cancer Institute in Bethesda, Maryland points out, “if these data confirm the findings of this trial, then we will certainly feel secure that an important breakthrough has been made.”

METASTATIC PANCREATIC CANCER

Single agents have only modest activity as treatment for metastatic pancreatic cancer with response rates of less than 10% and median survival rates of less than six months. Evaluations of single-agent gemcitabine and rubitecan as second-line treatment for relapsed pancreatic cancer have reported good patient tolerability and median survivals of 3.85 months and 4.7 months, respectively. Regimens incorporating two drugs have demonstrated encouraging activity and clinical impact compared with single-agent therapy. G-FLIP (gemcitabine, 5-fluorouracil, leucovorin, and cisplatin) is a regimen designed to incorporate four active single agents into a tolerable and active combination. A retrospective analysis evaluated the efficacy and safety of the G-FLIP regimen as second-line chemotherapy in a series of consecutively treated patients with metastatic pancreatic cancer.

G-FLIP was administered over 48 hours and repeated every two weeks. Day-one treatment consisted of sequentially administered gemcitabine 500 mg/m², irinotecan 80 mg/m², leucovorin 300 mg, and a 5-fluorouracil (5-FU) 400 mg/m² bolus, followed by an infusion of 5-FU 600 mg/m² over eight hours. Day-two treatment consisted of leucovorin 300 mg and a 5-FU 400 mg/m² bolus, followed by cisplatin 50 to 75 mg/m², and then an infusion of 5-FU 600 mg/m² over eight hours.

Thirty-four patients with histologically confirmed metastatic pancreatic cancer were consecutively treated. The median patient age was 64.5 years (range= 41–82 years) and all patients had objective disease progression on prior therapy; 32 patients had disease progression with gemcitabine, and 31 had disease progression with a gemcitabine/5-fluorouracil/cisplatin combination. Grade 3 to 4 hematological toxicities included anemia (23%), thrombocytopenia (53%), and neutropenia (38%). There were no grade 3 to 4 neutropenic fevers, treatment-related mortalities, or withdrawals. Nonhematological grade 3 to 4 toxicities were rare: nausea/vomiting (3%), neurotoxicity (3%), nephrotoxicity (6%), and diarrhea (3%). A partial response (PR) was attained in eight patients (24%) and seven patients had stable disease (SD). Seven and six patients who attained a PR or SD.

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respectively, had disease progression with prior gemcitabine-based therapy. The median time to disease progression for all 34 patients was 3.9 months, and 5.9 months for the eight patients who attained a PR. Median overall survival for all 34 patients was 10.3 months.

It was concluded that adding a single new drug such as irinotecan to the same first-line chemotherapy combination upon disease progression might be an important alternative to switching to different drug classes for treatment of relapsed/resistant cancer. The promising clinical outcomes and moderate toxicity associated with G-FLIP in this heavily pretreated group warrant development of this novel regimen, including tests as first-line therapy in patients with diseases likely to be responsive to the drugs contained in this combination.

**ADVANCED COLORECTAL CANCER**

Raltitrexed, a specific thymidilate synthase inhibitor, was evaluated in patients with advanced colorectal cancer (ACC) in relapse (> eight weeks) after a prior response or disease stabilization to first-line chemotherapy combination with irinotecan plus 5-FU plus leucovorin (LV). Twenty-five patients with metastatic ACC entered the pilot trial: 17 males and eight females. The median age was 61 (range= 47–70), median Karnovsky PS: 80 (70–90), and a life expectancy of at least three months. The sites of metastases were liver, 12; lung, 4; lymph nodes, 7; and peritoneal, 5. All patients had progressed after prior chemotherapy with irinotecan plus 5-FU plus leucovorin (LV). Raltitrexed was administered intravenously (IV) at a dose of 3 mg/m² every 21 days.

Three patients (12%) achieved a partial response (PR), eight (32%) had stable disease (SD), and the remaining 14 (56%) developed progressive disease (PD). Median time-to-progression (TTP) was 5.5 months (range= 2–8.5), and median overall survival (OS) was eight months (range: 4–12.5). Toxicity was generally mild and consisted mainly of myelosuppression; neutropenia grade 1 to 2: 52%; grade 3: 28%; and anemia grade 1 to 2: 36%. Mild mucositis, grade 1 to 2, occurred in 13.5% of patients and was the principal non-hematologic toxicity. Response to treatment with raltitrexed is limited in patients with ACC failing after an initial response or non-progression to the weekly irinotecan plus 5-FU plus LV combination. It appears that a limited number of patients with PR/SD might derive clinical benefit, but final proof would require a large, randomized study.

**ADVANCED GASTRIC CANCER**

Many phase II studies have reported improved response rates with severe toxicity of etoposide, doxorubicin (Adriamycin, Pharmacia), and cisplatin in advanced gastric cancer. In an attempt to obtain a better regimen with high efficacy and less toxicity, a combination regimen of etoposide, doxorubicin, and carboplatin (EAC) had been developed and evaluated in this phase II study. Forty-six patients with advanced gastric cancer were enrolled in the study. The treatment consisted of doxorubicin 20 mg/m² IV on days one and seven, etoposide 70 mg/m² IV on days four, five, and six, and carboplatin 200 mg/m² IV on days two and eight. Therapy was repeated every four weeks. Patients with stable disease or who responded received an additional two to six cycles of therapy.

Among 45 patients evaluated for response and toxicity, there was a 49% objective response rate, including 7% complete remission and 42% partial response. There was 11% stable disease and 27% progressive disease. Among 11 patients with lymph node metastasis only after a curative gastrectomy, there was an 82% objective response rate, with 27% having complete remission and 55% having partial response.

The median follow-up was 16 months; the median survival duration of all 45 patients was 11 months. The median time to progression was five months. The main toxicity was myelosuppression, with a high incidence of 82% leukopenia—but only 9% of grades 3 to 4. Gastrointestinal toxicity was mild, with a low incidence of 42% nausea and vomiting and only 2% of grades 3 to 4. There were no chemotherapy-related deaths. With mild and tolerable toxicity, the EAC regimen has active anti-tumor activity in advanced gastric cancer, which might have a positive influence on long-term survival time. It has a high efficacy, especially in patients with lymph node metastasis only after a curative gastrectomy. This regimen deserves further clinical studies for testing activity and toxicity in patients with advanced gastric cancer.

**REFRACTORY LEUKEMIA**

A study was carried out to investigate the activity of a novel dioxolane L-nucleoside analog, troxacitabine (L(-)-OddsC, BCH-4556), in patients with refractory leukemia. Troxacitabine is a novel nucleoside analog developed by BioChem Pharma. Troxacitabine (BCH-4556) is the first nucleoside with the unnatural β-L-configuration shown to have anticancer activity. Unlike cytosine arabinoside ( AraC), this cytosine analog is active against both solid and lymphoid tumors in vivo. Although troxacitabine shares a common metabolic pathway for activation with AraC and gemcitabine, it is unlike those two compounds in that it is not converted to an inactive compound by cytidine deaminase. It might therefore be effective in malignant disease in which deamination is a major mechanism of resistance. In addition, troxacitabine is active in cell lines refractory to gemcitabine because of impaired transport, and it is a potent inhibitor and chain terminator of human cellular DNA polymerases. Troxacitabine has demonstrated substantial preclinical activity against human renal cancer cell lines grown in nude mice. Responses were previously observed in patients with kidney cancer when administered every three weeks.

In the present study, participants were patients with refractory or relapsed acute myeloid (AML) or lymphocytic (ALL) leukemia, myelodysplastic syndromes (MDS), or chronic myelogenous leukemia in blast phase (CML-BP). Troxacitabine was provided as an intravenous infusion for more than 30 minutes daily for five days at a dose of 8 mg/m²/day (40 mg/m² per course). Courses were given every three to four weeks according to antileukemic efficacy.
Forty-two patients (AML, 18 patients; MDS, one patient; ALL, six patients; CML-BP, 17 patients) were treated. Median age was 51 years (range= 23–80 years); 22 patients were male. Stomatitis was the most significant adverse event, with three patients (7%) and two patients (5%), respectively, experiencing grade 3 or 4 toxicity. Ten patients (24%) had grade 3 hand–foot syndrome, and two patients (5%) had grade 3 skin rash. One patient (2%) had grade 3 fatigue and anorexia. Marrow hypoplasia occurred between days 14 and 28 in 12 (75%) of 16 assessable patients with AML. Two complete remissions and one partial remission (18%) were observed in 16 assessable patients with AML. None of six patients with ALL responded. Six (37%) of 16 assessable patients with CML-BP experienced a return to chronic-phase disease. The results of the study showed that troxacitabine had significant antileukemic activity in patients with AML and CML-BP.

REFERENCES