

Preoperative Chemoradiotherapy May Improve Overall Survival Over Chemotherapy Alone in Locally Advanced Adenocarcinoma

Findings from a phase III study showed significant improvement in overall survival (OS) and tumor-free survival with chemoradiation over chemotherapy alone in patients with localized esophagogastric adenocarcinoma. These findings, conducted by the German Oesophageal Cancer Study Group and reported in the January 12 issue of *Journal of Clinical Oncology*, were based on data from 119 of 126 patients who were 70 years or younger.

Patients who had type I to III adenocarcinoma of the esophagogastric junction were enrolled in the study from November 2000 to December 2005. Fifty-nine patients were randomized to receive chemotherapy, and 60 patients received chemoradiation. Treatment in the chemotherapy arm included induction and subsequent treatment with cisplatin, fluorouracil, and leucovorin. Treatment in the chemoradiotherapy group consisted of the same induction followed by cisplatin, etoposide and a radiation dose of 30Gy. The number of patients requiring surgery was similar between the 2 treatment groups. In the chemotherapy group, 41 of 59 patients (69.5%) underwent complete resection; in the chemoradiotherapy group 43 of 60 patients (72%) had surgery. Of the 94 evaluable patients, the complete pathohistologic response rate was significantly higher in the chemoradiotherapy group than in the chemotherapy group (15.6% vs 2.0%; $P=.03$). This observation was also seen in the proportion of patients with tumor-free lymph nodes (64.4% vs 36.7%; $P=.01$). After a median follow-up of 45.6 months, 30 patients in the chemoradiotherapy group and 38 patients in the chemotherapy group had died. In patients receiving chemoradiotherapy, grade 3/4 leukocytopenia was reported in 12% of patients and grade 3/4 thrombocytopenia was reported in 5%. Median OS was 12 months longer in patients receiving chemoradiotherapy than in patients receiving chemotherapy (33.1 months vs 21.1 months), and the 3-year OS (47.4% vs 27.7%; $P=.07$) and 3-year local tumor progression (76.5% vs 59%; $P=.06$) rates favored chemoradiotherapy as well. Although the study was terminated early due to a lack of patient accrual, the findings suggest that preoperative chemoradiotherapy may improve OS over chemo-

therapy alone. Further study of chemotherapy, targeted therapy, and radiation therapy is needed.

Researchers Discover Breast Cancer Gene Linked to Metastasis

A group of researchers from Princeton University and The Cancer Institute of New Jersey have identified a gene that switches on in 30–40% of all breast cancer patients, spreading the disease and ultimately causing death. Their work is reported in the January 6 issue of *Cancer Cell*. The gene, called Metadherin (MTDH), was found in a small region of human chromosome 8. Investigators claimed that MTDH appears to be the culprit of metastasis because it helps tumor cells stick tightly to blood vessels in distant organs.

The study, led by Yibin Kang, PhD, assistant professor of molecular biology at Princeton University, found that the gene also increases resistance to chemotherapeutic agents frequently used to combat breast cancer. The inhibition of MTDH will reduce the chance of recurrence as well as the risk of metastasis. The discovery of MTDH is based on 3 years' worth of work utilizing an approach that combined integrative genomics with clinical research and laboratory experimentation. The scientists re-analyzed clinical breast cancer databases and found that one region in particular—8q22—was repeated as many as 8 times in the genomes of poor prognosis breast tumors. The researchers went on to find that among the genes in the 8q22 region, MTDH was responsible for the aggressive behavior of poor-prognosis tumors. The researchers also found that tumors that overexpress MTDH are more likely to metastasize to the lungs, along with other vital organs and bones and are more resistant to agents such as paclitaxel, cisplatin, and doxorubicin. However, when cancer cells were genetically altered to reduce MTDH expression, they became less metastatic to other organs and less resistant to chemotherapeutic agents. Researchers suggested that MTDH may also be involved in the progression of other cancers, such as prostate cancer, and concluded that by using the multidisciplinary research strategy used to find this gene, it is likely they can also find other genes involved in the spread of cancer.

(Continued on page 87)

Adjuvant LV5FU2 Plus Irinotecan in Patients With High Risk of Relapse Showed No Improvement in DFS and OS

A multicenter adjuvant phase III trial that evaluated the addition of irinotecan to LV5FU2 in colon cancer patients at high risk of relapse showed it had little benefit.

The study, led by Marc Ychou, MD, PhD, and published in the January 29 issue of *Annals of Oncology*, investigated a total of 400 patients with histologically proven primary colon cancer. The patients were randomized to LV5FU2 (leucovorin 200 mg/m², 2-hour infusion, 5-fluorouracil [5-FU] 400 mg/m² bolus, 600 mg/m² 22-hour continuous infusion on days 1 and 2) or LV5FU2 plus IRI (irinotecan; 180 mg/m² 90-min infusion on day 1 + LV5FU2) fortnightly for 12 cycles. The primary endpoint was disease-free survival (DFS).

At a median follow-up of 63 months, significantly more T4 tumors and 15 or more positive lymph nodes were observed in the LV5FU2 plus IRI arm. The relative dose intensity for 5-FU was greater than 0.80 for 94% and 77% of patients in the LV5FU2 alone and LV5FU2 plus IRI arm, respectively ($P < .001$). Irinotecan relative dose intensity was greater than 0.80 for 70% patients. There was more grade 3/4 neutropenia in the LV5FU2 plus IRI arm (4% vs 28%; $P < .001$). The 3-year DFS was 60% (95% confidence interval [CI], 53–66%) in the LV5FU2 arm, and 51% (95% CI, 44–58%) in the LV5FU2 plus IRI arm. There was no difference when adjusted for prognostic factors (hazard ratio=1.12, 95% CI, 0.85–1.47, $P = .42$). The 5-year OS was 67% (95% CI, 59–73%) and 61% (95% CI, 53–67%) in the LV5FU2 alone and LV5FU2 plus IRI arm, respectively. Researchers therefore concluded that adjuvant LV5FU2 plus IRI compared with LV5FU2 alone in patients at high risk of relapse showed no improvement in DFS and OS.

Positive Long-term Outcomes in Treating Pediatric Acute Promyelocytic Leukemia

Long-term results from 3 clinical trials, presented at the 2008 annual meeting of the American Society of Hematology, showed encouraging outcomes when children with acute promyelocytic leukemia were treated with all-trans retinoic acid (ATRA) and anthracycline monotherapy. The study included patients younger than 19 years from studies LPA96, LPA99, and LPA2005 conducted by the Programa de Estudio y Tratamiento de las Hemopatías Malignas group.

For induction therapy, patients received 25 mg/m² of ATRA daily until complete response (CR), and 12 mg/m² of idarubicin on days 2, 4, 6, and 8. In the LPA96 trial, patients who received CR underwent 3 monthly chemotherapies. In the subsequent LPA99 trial, idarubicin doses in the first and third courses were increased for patients with an intermediate or high risk of relapse; 25 mg/m² of ATRA was given simultaneously in all 3 courses. In the ongoing LPA2005 trial, consolidation therapy was further modified and includes ATRA to all patients and reduced mitoxantrone for low- and intermediate-risk patients in the second course from 5 to 3 days. For high-risk patients, cytarabine was added to idarubicin in the first and third courses.

Nearly 95% of the pediatric patients achieved a CR. Toxicity was generally manageable during consolidation and maintenance therapy. Therefore, scientists concluded that the study, led by investigator Luis Madero, MD, of Niño Jesús Children's Hospital in Madrid, showed high antileukemic efficacy with a relatively low toxicity and a high degree of compliance. There was a high incidence of headache and pseudotumor cerebri, but none that was unmanageable or affected mortality.