TPF better than PF regimen for HNC

A THREE-DRUG treatment for head and neck cancer (HNC) improves long-term survival so significantly that researchers are calling for the trio to become the standard of care for patients suitable for first-line therapy.

The study that yielded this positive news was a long-term look at the TAX 324 open-label, randomized phase 3 trial. The original project compared three cycles of induction chemotherapy with docetaxel (Taxotere), cisplatin (Platinol, generics), and fluorouracil—a regimen referred to as TPF—versus cisplatin and fluorouracil (PF) in the treatment of locally advanced (stage III or IV) head and neck cancer.

Locally advanced squamous cell carcinoma (SCC) of the head and neck is potentially curable in most patients, but only about half live for 3 years after standard therapy, and 40% to 60% eventually develop locoregional recurrences, distant metastases, or second primary tumor. Initial results from the TAX 323 trial in unresectable disease and the TAX 324 trial in both resectable and unresectable disease have shown that adding docetaxel to PF induction chemotherapy increases survival in locally advanced head and neck cancer over a median of 42 months' follow-up (minimum of 2 years' follow-up).

Jochen H. Lorch, MD, MSc, of the Dana-Farber Cancer Institute in Boston, Massachusetts, and others working on behalf of the TAX 324 Study Group sought to determine whether the survival benefit endured beyond the follow-up period used in the initial analysis. This information is important because as Dr. Lorch and fellow researchers note in *The Lancet Oncology*, "5-year analyses have often revealed reduced survival and changes in outcomes in trials in head and neck cancer."

Three cycles of induction chemotherapy with TPF improves long-term survival in patients with locally advanced HNC.

PF patients received intravenous cisplatin 100 mg/m^2, followed by fluorouracil 1,000 mg/m^2 per day as a continuous 24-hour infusion for 5 days. TPF patients received docetaxel 75 mg/m^2 followed by intravenous cisplatin 100 mg/m^2 and fluorouracil 1,000 mg/m^2 per day, infused continuously over 24 hours for 4 days. The induction chemotherapy was given every 3 weeks for three cycles, with chemoradiotherapy beginning 3 to 8 weeks after the start of the third cycle.

A total of 501 participants had been recruited from 55 centers across the United States, Canada, Argentina, and Europe between May 21, 1999, and December 3, 2003. In the initial analysis of December 2005, 267 patients were still living and 234 had died. At that point induction chemotherapy with TPF was shown to significantly improve survival compared with PF.

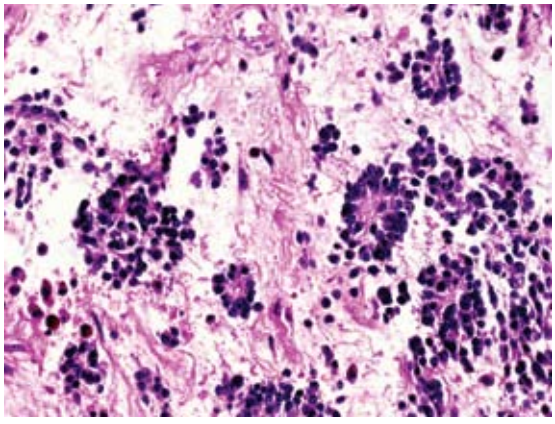
By December 1, 2008, 171 patients were still alive, 35 more had died, and 61 were lost to follow-up. Because Dr. Lorch and co-investigators found no sufficient evidence that loss to follow-up equated to death, they deemed those 61 people to be alive, and used their information from the initial analysis in 2005 for the updated assessment.

During a minimum follow-up period of 5 years (median: 6 years), "the survival advantage seen in the original report was sustained," affirmed Dr. Lorch's team. Overall survival was 26% better after treatment with TPF versus PF: Estimated 5-year survival rate was 52% in the TPF group and 42% in the PF group. Median survival was 70.6 months and 34.8 months, respectively.

The investigators point out that their study had several limitations: TAX 324 was a prospective, randomized trial, but the data for this follow-up analysis were gathered retrospectively. Survival information was available for 88% of the participants, but reliable data on tracheostomy and gastric feeding tubes were difficult to obtain for all patients, restricting interpretation of results.

The authors contend that patients who are candidates for induction chemotherapy should be treated with TPF. ■

New method detects residual cancer cells



Tumor cells (dark purple) in typical rosette-shaped arrangements

A PERSONALIZED diagnostic tool described as "powerful and nevertheless feasible" can detect and quantify human neuroblastoma cells in human blood and bone marrow samples.

Although detecting and quantifying the cancer cells that remain after treatment or that have migrated to new malignant sites is a powerful predictor of patient survival, few diagnostic strategies for identifying small numbers of these cancer cells exist. However, the work of a team led by Axel Weber at the Children's Hospital, University of Leipzig, in Leipzig, Germany, has advanced this effort (*J Clin Invest.* doi:10.1172/JCI44415).

Evidence from hematologic malignancies indicates that a very small residual population of tumor cells during or after therapy can significantly influence patient outcomes.

The Weber team studied primary solid-tumor specimens from 40 children with neuroblastomas. The scientists focused on amplicons, characteristic duplications of genomic regions within cancer cells. Mapping amplified genomic regions around *MYCN* yielded blueprints in the form of amplicon fusion sites (AFS) bridging polymerase chain reaction (PCR) assays. "These assays were absolutely tumor cell specific and capable of detecting one tumor cell in 1×10^6 to 8×10^6 control cells," wrote the investigators.

They concluded that once established from tissue of the primary tumor site, an individual AFS-PCR can track tumor cells or tumor cell DNA in potential metastatic sites of any tissue origin as well as in bone marrow aspirates, peripheral blood samples, and even in cerebral fluid, urine, or any other patient sample. ■

IMRT a less toxic form of radiation in anal cancer

A NOVEL chemoradiation regimen for the treatment of anal cancer is proven to have fewer significant side effects than conventional therapy while remaining just as effective.

The 2-year outcomes for dose-painted intensity-modulated radiation therapy (DP-IMRT) with 5-fluorouracil (5FU) and mitomycin C (MMC) used in the Radiation Therapy Oncology Group (RTOG) trial 0529 were similar to those seen in the 5FU/MMC/conventionally delivered radiation arm of RTOG 9811. The latter regimen is the standard of care for US patients with nonmetastatic squamous cell cancer of the anal canal. However, as RTOG 0529 principal investigator Lisa Kachnic, MD, chair of radiation oncology at Boston University, has stated, the treatment results in long-term disease-free survival but is associated with significant acute toxicity, partially due to the large radiation fields used.

IMRT conforms, or "paints," the radiation dose to the tumor and lymph nodes, sparing healthy surrounding tissue.

Conventionally delivered radiation therapy involves two- or three-dimensional fields that treat normal as well as diseased organs. In contrast, IMRT conforms, or "paints," the radiation dose to the tumor and lymph nodes, sparing healthy surrounding tissue.

An outcomes analysis of 52 patients with stage II or stage III anal cancer who had been treated with IMRT and 5FU/MMC chemotherapy showed overall survival was 86% and 2-year disease-free survival was 77% after a 26.7-month median follow-up period. These rates were comparable to the 2-year overall and disease-free survival rates of 91% and 75%, respectively, seen among the 325 patients who underwent conventional radiation with 5FU/MMC in RTOG 9811.

The difference, however, was in the side effects: The use of IMRT was associated with significantly less grade 3+ gastrointestinal and dermatologic acute toxicity. "Because of the associated acute toxicity sparing, DP-IMRT will be used as the platform, and may allow for radiation dose escalation, in future RTOG anal canal trials," noted the research group. ■

Morphine sulfate label revised to avoid dosing errors

ROXANE LABORATORIES has made labeling and product-packaging changes to its morphine sulfate oral solution 100 mg per 5 mL (20 mg/mL) due to accidental overdoses that resulted in adverse events and deaths. The product is indicated for the relief of moderate to severe acute and chronic pain in opioid-tolerant patients.

Roxane had marketed a morphine sulfate oral solution in a strength expressed as 20 mg/mL. That container label and carton labeling carried brown lettering on a white background. Now, a bright-yellow background is being used on multiple sides of the morphine sulfate oral solution 100 mg per 5 mL (20 mg/mL) to differentiate it from other such solutions with a white background marketed by the company. White lettering on a red background is used to present the drug name, strength, and concentration. The strength is presented as 100 mg per 5 mL, followed by a less prominently displayed concentration of "(20 mg/mL)."

A bright-yellow background is being used on multiple sides of the morphine sulfate oral solution 100 mg per 5 mL (20 mg/mL)

The new label also carries a boxed warning stating: only for use in patients who are opioid tolerant. Another boxed warning refers to the risk of accidental overdose and deaths caused by the confusion between different concentrations and between "mg" and "mL." These and other product labeling and packaging changes have been made to help reduce the risk of medication errors.

According to Roxane and the FDA, which notified oncology, pharmacy, and pain management practitioners to the usage errors in conjunction with the manufacturer, in most cases the solutions ordered in milligrams were mistakenly interchanged for milliliters. The Roxane letter, which includes a complete description of the changes to the carton, container, and packaging of the 100 mg per 5 mL (20 mg/mL) morphine sulfate oral solution, reminds providers to read the instructions in the medication guide and to discuss the correct use of the oral syringe with patients. ■

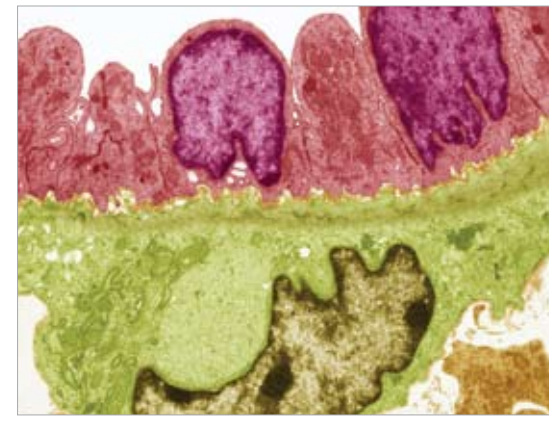
Endothelial cells may hold key to tumor malignancy

THE RECENT discovery that endothelial cells may be powerful regulators of tumors paves the way for a new approach to cancer treatment based on tissue engineering.

The endothelial cells that line blood vessels are especially prevalent in tumors, but their role within that environment has not been as well-understood as that of fibroblasts, immune cells, or other cells that help regulate cancer growth and metastasis. To learn more, Elazer R. Edelman, MD, PhD, of the MIT (Massachusetts Institute of Technology)–Harvard Division of Health Sciences and Technology, and associates placed endothelial cells right next to tumors, allowing the researchers to directly observe the interaction between these cells and cancer cells independent of blood flow.

The healthy endothelial cells secreted multiple molecules that made breast and lung cancer cells less proliferative and aggressive by reducing the molecular signals that drive these processes. These actions support the concept that endothelial cells are paracrine cancer regulators, and their signals can directly regulate tumor tissue.

"If endothelial cells are in fact an essential regulator of cancer growth, tumor aggressiveness might then be defined by whether endothelial cells or cancer cells can dominate (more aggressive tumors are able to overcome their endothelial cells while the more benign cannot)," noted a statement explaining the implications of the findings, which were published in *Science Translational Medicine* (2011;3[66]:66ra5). In their own report, the researchers state that the potential of endothelial cells to regulate cancer biology begs further study. ■



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Cuboidal endothelial cells (upper layer) lining a high endothelial venule.