

Cetuximab Improves Survival of Patients with Head and Neck Cancer

Adding cetuximab (Erbix, ImClone/Bristol-Myers Squibb) to a platinum-based chemotherapy regimen as first-line treatment for patients with recurrent or metastatic squamous-cell carcinoma of the head and neck may improve overall survival, according to a report in the September 11 issue of *The New England Journal of Medicine*. Previous studies have found cetuximab to be beneficial in treating patients with platinum-resistant recurrent or metastatic head and neck cancer; however, it was undetermined whether combining this drug with platinum-based therapy was effective.

The study, led by Jan B. Vermorken, MD, PhD, of the University of Antwerp, randomized 442 patients to receive platinum-fluorouracil chemotherapy alone or combined with cetuximab as first-line treatment. Researchers evaluated survival and other outcomes such as response rate. Findings showed that the addition of cetuximab increased the median overall survival (OS) from 7.4 to 10.1 months ($P=.04$). Similarly, progression-free survival (PFS) and the treatment response rate also increased from 3.3 to 5.6 months ($P=.001$) and from 20% to 36% ($P<.001$), respectively.

Safety analyses showed that neutropenia, anemia, and thrombocytopenia were the most common serious (grade 3/4) adverse events in both groups. Sepsis was a more common finding in the cetuximab group, compared to the control group (9 vs 1 patients; $P=.02$). Skin reactions (grade 3) were present in 9% of patients treated with cetuximab, and infusion-related reactions (grade 3/4) were seen in 3% of patients given cetuximab. There were no deaths attributed to cetuximab therapy.

Rituximab Combo Active Against Chronic Lymphocytic Leukemia

More than two-thirds of patients with chronic lymphocytic leukemia (CLL) who are receiving fludarabine, cyclophosphamide, and rituximab (Rituxan, Biogen Idec/Genentech) treatment will be able to achieve complete remission with no identifiable disease, researchers reported in the August 15 issue of *Blood*.

The study proved that the initial success of these agents is maintained in long-term treatment. Michael J. Keating, MD, of M.D. Anderson, and colleagues monitored 300 patients for 6 years; findings showed a 95% response rate and complete remission in 72% of patients. Six-year OS was 70% and failure-free survival (FFS) was 51%. The median time to progression was approximately

6 years and 8 months; 2 patients died within 3 months of starting therapy. Certain factors correlated to poor response to therapy were: age (at least 70 years old), presence of chromosome 17 abnormalities, or elevated serum lactate dehydrogenase.

Favorable-risk patients had a 6-year complete remission and a FFS rate of 84%. Late infection was present in 10% of patients in the first year of remission, but decreased significantly the second year (4%) and thereafter (1.5%). "The regimen has the highest complete remission rate, longest remission duration, and most favorable survival of frontline regimens for the treatment of CLL reported to date," the investigators stated. Results also showed that adding rituximab to chemotherapy regimens is cost-effective in terms of improvement of quality of life years.

Novartis Cancer Drug (Everolimus) Wins US Priority Review

The investigational drug RAD001 (ie, everolimus), manufactured by Novartis, has been given priority review in the United States for the treatment of advanced kidney cancer. The drug is an orally administered inhibitor of the mammalian target of rapamycin (mTOR), and works by disrupting the growth, division, and metabolism of cancer cells; it is to be sold under the brand name Afinitor.

Everolimus was granted accelerated review because phase III study results, reported in the August 9 issue of *Lancet*, found that it more than doubled the length of time without tumor growth and decreased the risk of disease progression by 70% in patients who failed standard treatment. The length of the review process was shortened from 10 to 6 months, due to this potential benefit to patients.

Robert Motzer, MD, of the Memorial Sloan-Kettering Cancer Center, and colleagues, randomized patients with metastatic renal cell carcinoma who failed sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer/Onyx Pharmaceuticals), or both, to receive everolimus 10 mg once daily ($n=272$) or placebo ($n=138$); primary endpoint was PFS, which was more than double in patients receiving everolimus (4 months) compared to those receiving placebo (1.9 months). The study was to be terminated after 290 events of progression, but was actually terminated after 191 progression events (101 [37%] events in everolimus group; 90 [65%] events in placebo group) because a significant difference in efficacy was observed between the 2 treatment groups. Although more adverse events were reported in patients receiving everolimus, most were mild or moderate in severity. This new drug is also being

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tested in other forms of cancer, including lymphoma and neuroendocrine tumors.

The Cancer Genome Atlas Reports Results of a Study of Brain Tumors

The first results of a large-scale study on glioblastoma were reported by the Cancer Genome Atlas (TCGA) Research Network in the September 4 issue of *Nature*. Glioblastoma, a type of brain cancer most commonly found in adults, is a very aggressive type of tumor.

The study involved sequencing 601 genes in glioblastoma samples donated by 206 patients and the matching of control tissue, which exposed 3 important genetic mutations that were not previously noted to be common in glioblastoma: mutations in the *NF1* gene, *ERBB2* gene, and *PIK3R1* gene. TCGA researchers also combined sequencing data with other types of genome characterization information in order to determine the core biological pathways involved in glioblastoma. There were 3 pathways identified, which were found to be disrupted in more than 3 quarters of glioblastoma tumors: the CDK/cyclin/CDK inhibitor/RB pathway, the p53 pathway, and the RTK/RAS/PI3K pathway. This pathway mapping showed to be informative in the development of therapeutic strategies directed at specific cancer; these 3 pathways were interconnected and coordinately deregulated in most of the glioblastoma tumors that were analyzed. Therefore, researchers pointed out that combination therapies aimed against the pathways may present an effective strategy for the treatment of these tumors.

In addition to these findings, a multi-dimensional analysis found that in patients with MGMT methylation, alkylating therapy might lead to mutations in genes that are crucial for DNA repair, also known as mismatch repair genes. These mutations lead to the emergence of recurrent tumors that contain a high number of DNA mutations, which may be resistant to chemotherapy treatment. If this mechanism is confirmed by further analysis, then first- or second-line treatments for these types of glioblastoma patients may include therapies that are designed to target the results of combined loss of MGMT and mismatch-repair deficiency. These findings may also assist researchers in finding the best way to merge alkylating chemotherapy drugs with next-generation targeted agents.

Immune System Proteins May Promote Tumor Growth

Proteins produced during an immune response may promote tumor growth rather than fight it, researchers at

the University of Pennsylvania School of Medicine have found. Protein C5a, part of the body's immune defenses against pathogens, was shown to help tumors build molecular shields against attacks by T-cells.

When the defense mechanism—the complement system—is activated, its proteins eradicate the body of microbes and foreign cells, and many cancer treatments are designed to boost this immune system to kill tumors. However, Maciej M. Markiewski, MD, PhD, and colleagues found that the activation of the complement system in tumor tissue leads to the generation of protein C5a, which attracts myeloid-derived suppressor cells (MDSC) to tumors. MDSCs block the function of CD8+ T cells, which normally dismantle a tumor. Moreover, researchers blocked the C5a receptor on cell surfaces and found tumor growth impaired at the same rate of paclitaxel.

Researchers concluded that depending on the specific tumor and the environment in which the tumors are developing, the complement system can promote tumor growth. Detailed findings can be found online September 28 in *Nature Immunology*.

Gene Variation of Fat Cell Protein Hormone Linked to Decreased Colorectal Cancer Risk

Consistent with previous studies that have linked obesity with the risk of colorectal cancer, Northwestern University Feinberg School of Medicine scientists have found that serum levels of adiponectin, a hormone secreted by fat tissue, are inversely correlated with obesity and high levels of insulin.

Virginia G. Kaklamani, MD, DSc, and colleagues conducted 2 case-control studies that included patients with a diagnosis of colorectal cancer and controls without cancer to investigate the association between variations of the adiponectin (ADIPOQ) and adiponectin receptor 1 (ADIPOR1) genes with colorectal cancer risk. Study 1 included 441 patients with colorectal cancer and 658 controls; study 2 included 199 patients with colorectal cancer and 199 controls, matched 1:1 for sex, age, and ethnicity.

Results and combined analysis of both studies showed an association between a single-nucleotide polymorphism [SNP]—a gene variation of the ADIPOQ gene (rs266729)—and colorectal cancer risk.

In conclusion, investigators suggest that the adiponectin axis may become an important modifier of colorectal cancer risk. Studies that address the potential impact of adiponectin and its SNPs in the prognosis of colorectal cancer are needed, they said. Findings are published in the October 1 issue of *JAMA*.