Chemotherapy Before Surgery Extends Life of Esophageal Cancer Patients

A study from researchers at the Medical Research Council’s Clinical Trials Unit in London suggests that compared with surgery alone, a short course of chemotherapy before surgery for esophageal cancer can significantly extend survival.

In a Phase III clinical trial of 802 patients—the largest of its kind in esophageal cancer—researchers found that patients who received preoperative chemotherapy for six weeks before surgery survived for a median of 17 months, compared to 13 months for patients treated with surgery alone. Two-year survival was 43 percent for patients treated with neoadjuvant chemotherapy and surgery compared to 34 percent for surgery alone.

“Preoperative chemotherapy offers a significant survival benefit and should be used before surgery,” said lead author Peter Clark, MD. Esophageal tumors tend to spread quickly beyond the esophageal wall. Neoadjuvant chemotherapy works by either shrinking the primary tumor and making it easier to remove, by eliminating microscopic clusters of tumor cells that have spread from the primary tumor to a lymph node or other area of the body (micrometastases), or both. Unlike previous trials that have used longer chemotherapy regimens without success, this study used a short course of chemotherapy.

Patients were treated with cisplatin, followed by fluorouracil. Each drug was delivered for a four-day period, followed by a two-week rest period. (Abstract # 502)

WHAT DOES THIS MEAN FOR PATIENTS?

Surgery is currently the standard of care for the disease. This study indicates that providing chemotherapy before surgery can shrink the cancer, thus facilitating the subsequent operation, as well as eliminate spread to other organs. People diagnosed with esophageal cancer should discuss this study with their doctor to see if they would benefit from preoperative chemotherapy.

New Drugs May Slow Prostate Cancer Metastases in Bone

In men with prostate cancer, approximately 30 percent eventually develop bone metastases, in which the cancer spreads, or metastasizes, to their bones. This can cause debilitating pain, and is the major cause of death in men with prostate cancer.

Two new drugs designed to block the spread of metastatic prostate cancer in bone appear to significantly slow the progression of cancer. In the first study, 244 patients with hormone-refractory prostate cancer (cancer that has stopped responding to hormone therapy) that had spread to the bones but who did not yet have associated symptoms received either an oral drug called ABT-627 (atrasentan) or a placebo.

Patients treated with ABT-627 experienced a longer time period before indicators such as imaging tests or onset of pain signaled further bone metastasis, compared with the group that received the placebo (198 days vs. 129 days, respectively), according to researchers at Johns Hopkins University.

The drug also doubled the time for prostate specific antigen tests to rise by more than 50 percent, which is a good indicator of slowing of disease progression.

“This is quite exciting because the data suggests this continued on page 3...”

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Antiangiogenesis drugs are among the new biological cancer therapies that target the underlying mechanisms that allow a tumor to grow. These drugs work by cutting off the blood supply of a tumor, essentially starving it.

One of the first studies on the use of the antiangiogenesis drug endostatin in advanced cancer patients shows that the drug is safe to administer, with no side effects at the highest doses. The study also found higher doses of the drug caused a decrease in blood flow.

Researchers from the University of Texas M.D. Anderson Cancer Center conducted a Phase I trial to determine how endostatin works and how safe it is at different doses; the trial was not designed to test the effectiveness of the drug. Although two patients experienced a small amount of anti-tumor activity, the cancer ultimately grew in all 25 patients tested. Tumor imaging showed that increasing doses of the drug were associated with decreased blood flow to tumors and reduced metabolic activity in the cancer. Biopsies of tumors from all patients before and after treatment showed increased cell death in both tumor cells and the cells that line nearby blood vessels, called endothelial cells.

‘Although all patients in this trial ultimately experienced disease progression, endostatin was well tolerated and had a good pharmacokinetic profile,’ said lead author Roy Herbst, MD. ‘Our ability to identify drug-related effects on tumors, blood vessels, and tumor blood flow also suggests that endostatin may have a role in the treatment of cancer.’

(Abstract # 9)
STI-571 Shows Remarkable Response in Solid Tumors

Results from two studies on a new drug called STI-571 for advanced gastrointestinal stromal tumors (GIST) suggest that therapies that are targeted at the molecular level can be remarkably effective in difficult-to-treat cancers.

STI-571 is a signal transduction inhibitor, a drug that acts like a “circuit breaker” to block specific enzymes that can send faulty signals to trigger tumor cell growth, thus preventing the signal from being activated. In GIST, STI-571 blocks the growth signal of a gene called c-kit that is overexpressed and promotes cell proliferation.

In the first study, STI-571 produced an 89 percent clinical improvement in patients with GIST. The Phase II clinical trial included 139 patients, of whom less than 1 percent had responded to previous therapies. Sixty-eight patients experienced a partial response and 54 patients had stable disease. “These results are very exciting and demonstrate the value of therapy that is molecularly targeted at what makes a cell cancerous,” said lead author Charles Blanke, MD, of Oregon Health Sciences University. “For the first time, STI-571 is showing tremendous benefit in a solid tumor.” (Abstract # 1)

The second study, a smaller, Phase I, dose-testing clinical trial conducted by the European Organization for Research and Treatment of Cancer’s Soft Tissue and Bone Sarcoma Group, also found that STI-571 resulted in clinical and radiological improvement in the majority of patients with GIST.

WHAT DOES THIS MEAN FOR PATIENTS?

This is the first study to evaluate the effectiveness of STI-571 (known as Gleevec) as a treatment for solid tumors, and results are extremely encouraging. A Phase III trial is the next step in determining whether STI-571 will be effective in treating gastrointestinal stromal tumors. STI-571 has also been shown to be effective in treating chronic myeloid leukemia (CML). The FDA approved Gleevec for use in treating CML on May 10, 2001.

QUICK FACTS

CLINICAL TRIALS

Clinical trials are designed to evaluate whether a new development is safe, effective, and better than the current standard of care. In the case of cancer, clinical trials have led to scientific advances that have increased doctors’ understanding of how and why tumors develop and grow.

Clinical trials are carried out in steps called phases. Each of the three phases is designed to find out different information.

Phase I trials gather data on dosage, timing, and safety—but not efficacy—of an investigational therapy. Phase I trials generally last several months to a year and usually involve a very small number of patients, usually no more than 10 to 20. Once there is a hint of response by a patient to a therapy, disease specific research can begin with a Phase II trial.

Phase II trials are designed to provide more detailed information about the safety of the treatment, as well as to evaluate the efficacy of the drug. They take approximately two years to complete and usually involve a small number of patients, typically 20 to 40. The response rate in this phase needs to be equal or higher than normal in order to proceed to Phase III trials.

Phase III trials compare a promising new treatment with the current standard of care. The number of patients enrolled in a Phase III trial can range in the hundreds to thousands. These trials may take many years to complete. Once a drug has been proven successful in a Phase III trial, an application for US Food and Drug Administration (FDA) approval can be submitted.

Prostate Cancer

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low-toxicity pill leads to clinical benefit and delays time before patients may need additional systemic treatments,” said lead author Michael Carducci, MD. (Abstract # 12)

The second study, a Phase III trial conducted by researchers at the Royal Marsden Hospital in Sutton, England, found that patients with advanced prostate cancer that had spread to the bone experienced a longer interval to bone pain, and perhaps an improvement in survival, using an oral drug called clodronate. A member of a class of drugs called bisphosphonates, clodronate relieves pain by inhibiting the abnormal absorption of bone tissue caused by spread of cancer cells, thereby allowing the bone to heal itself. (Abstract # 693)

WHAT DOES THIS MEAN FOR PATIENTS?

Given the limited treatment options for patients who have not responded to hormone therapy, these findings are important. These new drugs appear to offer palliative relief from painful bone metastases, improving quality of life and slowing the progression of cancer. Men who have prostate cancer should talk to their doctor about options that may help slow the spread of metastatic prostate cancer to bone.

QUICK FACTS

It is estimated that 198,100 new cases of prostate cancer will be diagnosed in the US this year, and 31,500 men will die from the disease.

Prostate cancer incidence rates are significantly higher in African-American men than in white men.

Prostate cancer is the second leading cause of cancer death in men.
The monoclonal antibody IMC-C225 causes tumors to shrink in some patients with advanced colorectal cancer who are no longer responding to standard treatment, according to a study by researchers at Memorial Sloan-Kettering Cancer Center.

Monoclonal antibodies are substances that can locate and bind to cancer cells wherever they are in the body. They can be used alone, or to deliver drugs, toxins, or radioactive material directly to tumor cells.

Patients with colorectal cancers that have become resistant to the standard drugs used to treat the disease, irinotecan (CPT-11) and fluorouracil (5-FU), have few treatment options. In this Phase II trial of 121 patients, patients who were taking CPT-11 and whose disease was getting worse were given the exact same dose and schedule of CPT-11 with the addition of IMC-C225, known as cetuximab. Tumors shrank by more than 50 percent in 23 percent of the patients using the combination of drugs.

“We achieved a remarkable response rate in this most resistant patient population,” said principal investigator Leonard Saltz, MD. “Now that we have shown that responses can be achieved in these resistant patients, we are excited about the possibility of using it in conjunction with first-line chemotherapy, before patients develop resistance.”

WHAT DOES THIS MEAN FOR PATIENTS?
IMC-C225 appears to block signals in the cancer cell that tell it to continue to grow and survive, leaving tumors more vulnerable to standard chemotherapy. Patients with colorectal cancer that has stopped responding to chemotherapy should talk with their doctor to determine the most appropriate treatment options for them. Further studies of IMC-C225 are ongoing in colorectal cancer, as well as in other cancers, including head and neck, pancreas, and lung cancers.
Nearly 80 percent of patients undergoing stem cell transplant for cancers of the bone marrow or lymph nodes develop mucositis, an inflammation of the mucous membranes that results in open sores or ulcers in the mouth. Patients with leukemia, lymphoma, Hodgkin’s disease, or multiple myeloma often cannot eat, drink, or talk for a week or more following chemotherapy, radiation, and blood stem cell transplant treatments.

A new treatment using an experimental human growth factor (definition) significantly improves the quality of life for these patients, according to a team of US and Canadian researchers. No effective therapy is currently approved for treatment of severe oral mucositis, which requires intravenous fluids and nutrition in the hospital as well as pain medications.

The use of the experimental recombinant human keratinocyte growth factor rHuKGF, or KGF, decreased the length of time patients suffered from severe oral mucositis by half, according to lead author Ricardo T. Spielberger, MD, of the City of Hope National Medical Center. In addition, patients needed significantly less opioid painkillers and had much less mouth and throat pain. (Abstract # 25)

WHAT DOES THIS MEAN FOR PATIENTS?
This study demonstrates that clinical investigators are making substantial progress in controlling the spread of bladder cancer, thereby increasing the chances of survival. In this study, survival rates were almost doubled compared to surgery alone. Patients with bladder cancer who are considering their treatment options may wish to discuss this study with their doctor to determine if they would benefit from pre-operative chemotherapy. At this time, surgery alone is the standard of care for bladder cancer.
LARYNGEAL CANCER

Treatment Combination Helps Preserve Voicebox in People with Laryngeal Cancer

Patients with locally advanced cancer of the larynx treated with a combination of chemotherapy and radiation preserve the use of their voicebox significantly longer than patients treated with traditional therapy, according to researchers at Johns Hopkins Oncology Center.

Standard therapy for locally advanced laryngeal cancer is chemotherapy followed by radiation, surgical removal of the larynx, or in some cases, radiotherapy alone.

‘Results from this study support that concomitant cisplatin and radiotherapy should now be the standard approach to spare the larynx from surgical removal,” said lead author Arlene Forastiere, MD. “This treatment offers significantly more patients the opportunity to preserve their voice.’

In this Phase III clinical trial, 547 patients with locally advanced laryngeal cancer (cancer which had not metastasized beyond the larynx) were randomly assigned to three treatment groups: chemotherapy followed by radiation, chemotherapy given at the same time as radiation therapy, radiation alone. The chemotherapy used in the trial was cisplatin and 5-fluorouracil (5-FU).

The researchers then calculated the number of patients in whom treatment did not work within two years and who required surgery to remove their larynx. They concluded that concomitant chemoradiotherapy provided the best results. Only 12 percent of patients in the concomitant chemoradiotherapy group required surgery, compared to 26 percent of patients treated with chemotherapy followed by radiation and 31 percent of patients treated with radiation alone. (Abstract # 4)

WHAT DOES THIS MEAN FOR PATIENTS?

This study suggests that the combination of chemotherapy and radiation therapy given together enables more patients to delay recurrences that would require having their larynx removed or to avoid having their larynx removed altogether. People with laryngeal cancer that has not spread beyond the larynx should discuss this treatment approach with their doctor to determine if it is more beneficial for them than the standard treatment.

APPETITE WEIGHT GAIN

Marijuana Derivative Less Effective in Stimulating Appetite and Weight Gain

The drug dronabinol, a derivative of marijuana, is not as effective as the standard treatment for improving waning appetites and increasing weight gain in cancer patients, according to researchers at the Mayo Clinic.

Depending on the location of the primary tumor, 60 to 80 percent of patients with advanced disease and 25 to 40 percent of patients with early disease experience cancer-related anorexia.

Dronabinol was tested against megestrol acetate, the drug traditionally used to treat cancer-related anorexia, as well as in combination with it. Megestrol acetate, a synthetic progesterone, or female hormone, was first used as a treatment for breast cancer and is now widely prescribed for weight gain.

The Phase III trial included 469 patients representing the spectrum of advanced cancers with the exception of breast cancer, gynecologic malignancies, and brain tumors. Seventy-three percent of the patients using megestrol acetate had improved appetites compared with 47 percent of the patients using dronabinol; 13 percent of the patients using megestrol gained weight, compared with 5 percent of the group using dronabinol. The patients using both of the stimulants did not have any greater improvement than the patients in the megestrol group.

‘Lack of appetite is a major problem that affects more than half of patients with advanced cancer,’ said the study’s lead author, Aminah Jatoi, MD. “It’s disappointing that dronabinol is not more helpful than megestrol acetate, which helps some cancer patients—but not all—regain their appetite.’ (Abstract # 1547)

WHAT DOES THIS MEAN FOR PATIENTS?

Although marijuana or its derivative products are commonly thought to be effective for these symptoms, this study demonstrates that the hormone Megace actually is more effective for improving appetite and weight gain.
BRAIN TUMORS

Female Brain Tumor Patients at Higher Risk for Divorce or Separation

Married female patients with brain tumors are dramatically more likely to experience a separation or divorce during the course of their illness than male patients, suggests a study from researchers at the Barrow Institute.

The researchers initially focused on patients with malignant gliomas, the most deadly type of brain tumor, and then looked at patients who had nervous system disease (multiple sclerosis) but did not have cancer, as well as at patients who had cancer other than brain cancer (breast cancer, lung cancer, lymphoma, and other types of cancer) but did not have nervous system disease, to see whether the same pattern of marital disruption was present.

In 214 patients with brain tumors, women were 8 times more likely to undergo separation or divorce. In 107 patients with multiple sclerosis, women were nearly 7 times more likely to suffer these outcomes. Finally, in 193 patients with other types of cancer, women were nearly 12 times more likely to report such problems.

Researchers were surprised at the much higher rate of marital disruption among female patients in all three disease groups, and were particularly alarmed at the “extraordinarily high” incidence of divorce among women with gliomas. From the time they are diagnosed with malignant gliomas, most patients survive only about a year, so these problems occurred rapidly and at a time when the patients were in most need of support. Comparatively, women in the other two groups were followed for years, sometimes longer than a decade.

“The number of failed marriages among women with brain tumors is very alarming, and suggests their male partners were not as supportive as one would hope,” said study leader Michael Glantz, MD. “Women seem to be more willing or more adept at nurturing their husbands through an illness, while men are not as skilled at doing the same for their wives.” (Abstract # 227)

Chemotherapy at the End of Life

A study of nearly 8000 Medicare patients reveals that approximately one-third of cancer patients receive chemotherapy in the last six months of life, even if the cancer is known to be unresponsive to treatment.

Researchers from the National Institutes of Health, Boston University School of Medicine and Stanford University School of Medicine could not determine whether chemotherapy was given in response to patient or family demand, or physician reluctance to acknowledge patients’ imminent death.

After examining Medicare data on cancer deaths in Massachusetts, the researchers concluded that responsive and unresponsive cancers were treated equally often with chemotherapy at the end of life. In the last six months of life, 33 percent of patients with pancreatic cancer, 30 percent of patients with melanoma, 30 percent of patients with breast cancer, and 32 percent of patients with colon cancer received chemotherapy. In the last month of life, the figures were 8 percent, 10 percent, 8 percent, and 7 percent, respectively. Breast, colon and ovarian cancers are chemotherapy-responsive, but melanoma, pancreatic, renal cell, hepatocellular, and gallbladder cancers are not chemotherapy-responsive cancers.

“While use of the chemotherapy in responsive cancers is understandable and may shrink the tumor and offer palliation, providing chemotherapy to patients with unresponsive cancers is hard to justify,” said the study’s lead author, Ezekiel Emanuel, MD, of the National Institutes of Health. “Providing chemotherapy at the same rate to tumors that are not chemotherapy-responsive as to those that are chemotherapy-responsive strongly suggests overuse of chemotherapy at the end of life.”

There are no standards for the appropriate use of chemotherapy at the end of life based on either randomized, controlled trials or expert, consensus guidelines.

The study also found that younger patients (ages 64-74) were treated more often with chemotherapy in their last months of life compared with older patients (ages 75-84). Unexpectedly, patients who received chemotherapy in the last 6 months of life were more likely to receive hospice care (38 percent versus 29 percent). However, patients who received chemotherapy at the end of life and also received hospice had fewer days in hospice. (Abstract # 953)

WHAT DOES THIS MEAN FOR PATIENTS?

Marital troubles can clearly impact a patient’s quality of life and treatment. This study highlights this issue for physicians and families and suggests that counseling may help spouses cope better with the seriousness of their partners’ illness. Follow-up studies are underway to see if marriage counseling or other interventions can help brain tumor patients and their spouses. Patients and their families should talk to their doctor about support services and other resources available in their communities.
Antidepressant Relieves Depression but Not Fatigue in Cancer Patients

The antidepressant Paxil significantly relieves depression in cancer patients undergoing chemotherapy but has less effect on fatigue, according to researchers who originally speculated that fatigue was linked to depression.

Results of the study, sponsored by the National Cancer Institute and conducted by community physicians nationwide, suggest that fatigue in these patients may be more related to the cancer and its treatment.

Previous studies in the general population and several surveys of cancer patients have associated depression with increased fatigue, and animal models of low serotonin levels have also demonstrated a common link.

Depression is associated with a decreased amount of serotonin in the brain, which helps regulate mood. Paxil blocks the reabsorption of serotonin and normalizes the brain’s chemical supply. In this study, patients received either a 20 mg daily dose of Paxil or a placebo. Patients were then asked to fill out questionnaires on mood and functioning.

“Up to half of cancer patients may experience some degree of depression during the course of their diagnosis, treatment and recovery, and the condition has not been optimally treated,” said lead author Gary Morrow, PhD, of the University of Rochester. (Abstract # 1531)

WHAT DOES THIS MEAN FOR PATIENTS?

This study demonstrates that depression can be treated successfully in cancer patients. It also shows that cancer fatigue is a separate entity for which an effective treatment still needs to be proven. Patients who are undergoing chemotherapy and are depressed should talk with their doctor about medications that can help them feel better. Patients experiencing fatigue should also talk with their doctor; since fatigue may be based more on their cancer and its treatment rather than on depression, the doctor may be able to recommend options to reduce fatigue.