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Cancer and the constitution: choice at life’s end
Annas, G.J. (2007)

Oscar the Cat awakens from his nap, opening a single eye to survey his kingdom. From atop the desk in the doctor’s charting area, the cat peers down the two wings of the nursing home’s advanced dementia unit. All quiet on the western and eastern fronts. Slowly, he rises and extravagantly stretches his 2-year-old frame, first backward and then forward. He sits up and considers his next move. In the distance, a resident approaches. It is Mrs. P., who has been living on the dementia unit’s third floor for 3 years now. She has long forgotten her family, even though . . .


It was Mr. G.’s third exacerbation of congestive heart failure in the past 6 months. Eighty-three years old, he had New York Heart Association class IV heart failure, end-stage coronary artery disease, and insulin-dependent diabetes. Although he had never wanted to be put on a ventilator, this time his shortness of breath was so terrifying that he felt he had no choice. After having a good response to diuresis, he was successfully extubated and transferred out of the coronary care unit. Two days later, a hospitalist suggested to Mr. G. and his wife that given his advanced disease, he should . . .


Although the numbers of organ donors and transplantations in the United States have more than doubled over the past 20 years (see line graph), the demand for organs continues to dwarf the supply. In 2006, there were about 29,000 solid-organ transplantations; as of June 2007, there were about 97,000 people on waiting lists for organ transplantation.


It was the first day of my cardiology subinternship, and I was trying to catch details of the 29-year-old patient’s complex history. Juan Perez, a heroin addict who had undergone aortic-valve replacement years earlier, had been admitted overnight after presenting to the emergency department with acute onset of fever, chills, anorexia, and malaise; he was thought to have infectious endocarditis and severe aortic insufficiency. He was Puerto Rican and spoke only Spanish, despite having lived in Boston for many years. Mr. Perez quickly became the focus of morning rounds. Through the open door, I glimpsed him half-lying on the hospital . . .


More Americans are choosing hospice for end-of-life care, but ironically, hospice patients increasingly are forced to give up effective palliative treatments along with aggressive medical intervention. For Joanne Doolin, a 64-year-old mother of three who spent her last 2 years of life fighting colon cancer that eventually made it impossible to eat, enrollment in hospice care involved a difficult trade-off: with only a few weeks left to live and her daughter’s wedding approaching, Doolin was forced to choose between entering hospice care and continuing to receive total parenteral nutritional support. Unfortunately, treatment options are often limited by the economic constraints . . .


Metastatic testicular tumors that have not been successfully treated by means of initial chemotherapy are potentially curable with salvage chemotherapy. We conducted a retrospective review of 184 consecutive patients with metastatic testicular cancer that had progressed after they received cisplatin-containing combination chemotherapy. We gave 173 patients two consecutive courses of high-dose chemotherapy consisting of 700 mg of carboplatin per square meter of body-surface area and 750 mg of etoposide per square meter, each for 3 consecutive days, and each followed by an infusion of autologous peripheral-blood hematopoietic stem cells; the other 11 patients received a single course of this treatment. In 110 patients, cytoreduction with one or two courses of vinblastine plus ifosfamide plus cisplatin preceded the high-dose chemotherapy. Of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up
of 48 months (range, 14 to 118). Of the 135 patients who received the treatment as second-line therapy, 94 were disease-free during follow-up; 22 of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 were disease-free. A total of 98 of 144 patients who had platinum-sensitive disease were disease-free, and 26 of 35 patients with seminoma and 90 of 149 patients with nonseminomatous germ-cell tumors were disease-free. Among the 184 patients, there were three drug-related deaths during therapy. Acute leukemia developed in three additional patients after therapy. Testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue, even when this regimen is used as third-line or later therapy or in patients with platinum-refractory disease.


Bronchiolitis, the most common infection of the lower respiratory tract in infants, is a leading cause of hospitalization in childhood. Corticosteroids are commonly used to treat bronchiolitis, but evidence of their effectiveness is limited. We conducted a double-blind, randomized trial comparing a single dose of oral dexamethasone (1 mg per kilogram of body weight) with placebo in 600 children (age range, 2 to 12 months) with a first episode of wheezing diagnosed in the emergency department as moderate-to-severe bronchiolitis (defined by a Respiratory Distress Assessment Instrument score. We enrolled patients at 20 emergency departments during the months of November through April over a 3-year period. The primary outcome was hospital admission after 4 hours of emergency department observation. The secondary outcome was the Respiratory Assessment Change Score (RACS). We also evaluated later outcomes: length of hospital stay, later medical visits or admissions, and adverse events. Baseline characteristics were similar in the two groups. The admission rate was 39.7% for children assigned to dexamethasone, as compared with 41.0% for those assigned to placebo (absolute difference, –1.3%; 95% confidence interval [CI], –9.2 to 6.5). Both groups had respiratory improvement during observation; the mean 4-hour RACS was –5.3 for dexamethasone, as compared with –4.8 for placebo (absolute difference, –0.5; 95% CI, –1.3 to 0.3). Multivariate adjustment did not significantly alter the results, nor were differences detected in later outcomes. In infants with acute moderate-to-severe bronchiolitis who were treated in the emergency department, a single dose of 1 mg of oral dexamethasone per kilogram did not significantly alter the rate of hospital admission, the respiratory status after 4 hours of observation, or later outcomes.


Selective cyclooxygenase inhibitors may retard the progression of cancer, but they have enhanced thrombotic potential. We report on cardiovascular adverse events in patients receiving rofecoxib to reduce rates of recurrence of colorectal cancer. All serious adverse events that were cardiovascular thrombotic events were reviewed in 2434 patients with stage II or III colorectal cancer participating in a randomized, placebo-controlled trial of rofecoxib, 25 mg daily, started after potentially curative tumor resection and chemotherapy or radiotherapy as indicated. The trial was terminated prematurely owing to worldwide withdrawal of rofecoxib. To examine possible persistent risks, we examined cardiovascular thrombotic events reported up to 24 months after the trial was closed. The median duration of active treatment was 7.4 months. The 1167 patients receiving rofecoxib and the 1160 patients receiving placebo were well matched, with a median follow-up period of 33.0 months (interquartile range, 27.6 to 40.1) and 33.4 months (27.7 to 40.4), respectively. Of the 23 confirmed cardiovascular thrombotic events, 16 occurred in the rofecoxib group during or within 14 days after the treatment period, with an estimated relative risk of 2.66 (from the Cox proportional-hazards model; 95% confidence interval [CI], 1.03 to 6.86; P=0.04). Analysis of the Antiplatelet Trialists’ Collaboration end point (the combined incidence of death from cardiovascular, hemorrhagic, and unknown causes; of nonfatal myocardial infarction; and of nonfatal ischemic and hemorrhagic stroke) gave an unadjusted relative risk of 1.60 (95% CI, 0.57 to 4.51; P=0.37). Fourteen more cardiovascular thrombotic events,
six in the rofecoxib group, were reported within the 2 years after trial closure, with an overall unadjusted relative risk of 1.50 (95% CI, 0.76 to 2.94; P=0.24). Four patients in the rofecoxib group and two in the placebo group died from thrombotic causes during or within 14 days after the treatment period, and during the follow-up period, one patient in the rofecoxib group and five patients in the placebo group died from cardiovascular causes. Rofecoxib therapy was associated with an increased frequency of adverse cardiovascular events among patients with a median study treatment of 7.4 months’ duration.


In a randomized, double-blind, placebo-controlled trial, we evaluated the efficacy of certolizumab pegol in 662 adults with moderate-to-severe Crohn’s disease. Patients were stratified according to baseline levels of C-reactive protein (CRP) and were randomly assigned to receive either 400 mg of certolizumab pegol or placebo subcutaneously at weeks 0, 2, and 4 and then every 4 weeks. Primary end points were the induction of a response at week 6 and a response at both weeks 6 and 26. Among patients with a baseline CRP level of at least 10 mg per liter, 37% of patients in the certolizumab group had a response at week 6, as compared with 26% in the placebo group (P=0.04). At both weeks 6 and 26, the corresponding values were 22% and 12%, respectively (P=0.05). In the overall population, response rates at week 6 were 35% in the certolizumab group and 27% in the placebo group (P=0.02); at both weeks 6 and 26, the response rates were 23% and 16%, respectively (P=0.02). At weeks 6 and 26, the rates of remission in the two groups did not differ significantly (P=0.17). Serious adverse events were reported in 10% of patients in the certolizumab group and 7% of those in the placebo group; serious infections were reported in 2% and less than 1%, respectively. In the certolizumab group, antibodies to the drug developed in 8% of patients, and antinuclear antibodies developed in 2%. In patients with moderate-to-severe Crohn’s disease, induction and maintenance therapy with certolizumab pegol was associated with a modest improvement in response rates, as compared with placebo, but with no significant improvement in remission rates.


In our randomized, double-blind, placebo-controlled trial, we evaluated the efficacy of certolizumab pegol maintenance therapy in adults with moderate-to-severe Crohn’s disease. As induction therapy, 400 mg of certolizumab pegol was administered subcutaneously at weeks 0, 2, and 4. Patients with a clinical response (defined as reduction of at least 100 from the baseline score on the Crohn’s Disease Activity Index [CDAI]) at week 6 were stratified according to their baseline C-reactive protein level and were randomly assigned to receive 400 mg of certolizumab pegol or placebo every 4 weeks. Among patients with a response to induction therapy at week 6 (428 of 668 [64%]), the response was maintained through week 26 in 62% of patients with a baseline C-reactive protein level of at least 10 mg per liter (the primary end point) who were receiving certolizumab pegol (vs. 34% of those receiving placebo, P<0.001) and in 63% of patients in the intention-to-treat population who were receiving certolizumab pegol (vs. 36% receiving placebo, P<0.001). Among patients with a response to induction therapy at week 6, remission (defined by a CDAI score of 5 or less) at week 26 was achieved in 48% of patients in the certolizumab group and 29% of those in the placebo group (P<0.001). The efficacy of certolizumab pegol was also shown in patients taking and those not taking glucocorticoids or immunosuppressants and in patients who had and those who had not previously taken infliximab. Infectious serious adverse events (including one case of pulmonary tuberculosis) occurred in 3% of patients receiving certolizumab pegol and in less than 1% of patients receiving placebo. Antinuclear antibodies developed in 8% of the patients in the certolizumab group; antibodies against certolizumab pegol developed in 9% of all patients who entered the induction phase. Patients with moderate-to-severe Crohn’s disease who had a response to induction therapy with 400 mg of certolizumab pegol were more likely to have a maintained response and a remission at 26 weeks with continued certolizumab pegol treatment than with a switch to placebo.
Atherosclerotic peripheral arterial disease is associated with an increased risk of myocardial infarction, stroke, and death from cardiovascular causes. Antiplatelet drugs reduce this risk, but the role of oral anticoagulant agents in the prevention of cardiovascular complications in patients with peripheral arterial disease is unclear. We assigned patients with peripheral arterial disease to combination therapy with an antiplatelet agent and an oral anticoagulant agent (target international normalized ratio [INR], 2.0 to 3.0) or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes; the second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention, or death from cardiovascular causes. A total of 2161 patients were randomly assigned to therapy. The mean follow-up time was 35 months. Myocardial infarction, stroke, or death from cardiovascular causes occurred in 132 of 1080 patients receiving combination therapy (12.2%) and in 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (relative risk, 0.92; 95% confidence interval [CI], 0.73 to 1.16; P=0.48). Myocardial infarction, stroke, severe ischemia, or death from cardiovascular causes occurred in 172 patients receiving combination therapy (15.9%) as compared with 188 patients receiving antiplatelet therapy alone (17.4%) (relative risk, 0.91; 95% CI, 0.74 to 1.12; P=0.37). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared with 13 patients receiving antiplatelet therapy alone (1.2%) (relative risk, 3.41; 95% CI, 1.84 to 6.35; P<0.001). In patients with peripheral arterial disease, the combination of an oral anticoagulant and antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications and was associated with an increase in life-threatening bleeding.

Patency or thrombosis of the false lumen in type B acute aortic dissection has been found to predict outcomes. The prognostic implications of partial thrombosis of the false lumen have not yet been elucidated. We examined 201 patients with type B acute aortic dissection who were enrolled in the International Registry of Acute Aortic Dissection between 1996 and 2003 and who survived to hospital discharge. Kaplan–Meier mortality curves were stratified according to the status of the false lumen (patent, partial thrombosis, or complete thrombosis) as determined during the index hospitalization. Cox proportional-hazards analysis was performed to identify independent predictors of death. During the index hospitalization, 114 patients (56.7%) had a patent false lumen, 68 patients (33.8%) had partial thrombosis of the false lumen, and 19 (9.5%) had complete thrombosis of the false lumen. The mean (±SD) 3-year mortality rate for patients with a patent false lumen was 13.7±7.1%, for those with partial thrombosis was 31.6±12.4%, and for those with complete thrombosis was 22.6±22.6% (median follow-up, 2.8 years; P=0.003 by the log-rank test). Independent predictors of postdischarge mortality were partial thrombosis of the false lumen (relative risk, 2.69; 95% confidence interval [CI], 1.45 to 4.98; P=0.002), a history of aortic aneurysm (relative risk, 2.05; 95% CI, 1.07 to 3.93; P=0.03), and a history of atherosclerosis (relative risk, 1.87; 95% CI, 1.01 to 3.47; P=0.05). Mortality is high after discharge from the hospital among patients with type B acute aortic dissection.

**SPECIAL ARTICLE**

Jain, T., Ruchi S. Gupta (2007). Trends in the Use of Intracytoplasmic Sperm Injection in the United States. *New England Journal of Medicine, 357(3), 241-257.* Intracytoplasmic sperm injection (ICSI) was initially developed as part of in vitro fertilization (IVF) to treat male-factor infertility. However, despite the added cost, uncertain efficacy, and potential risks of ICSI, its use has been extended to include some patients without documented male-factor infertility. We analyzed national data
The prevalence of obesity has increased substantially over the past 30 years. We performed a quantitative analysis of the nature and extent of the person-to-person spread of obesity as a possible factor contributing to the obesity epidemic. We evaluated a densely interconnected social network of 12,067 people assessed repeatedly from 1971 to 2003 as part of the Framingham Heart Study. The body-mass index was available for all subjects. We used longitudinal statistical models to examine whether weight gain in one person was associated with weight gain in his or her friends, siblings, spouse, and neighbors. These clusters did not appear to be solely attributable to the selective formation of social ties among obese persons. A person’s chances of becoming obese increased by 60% (95% confidence interval [CI], 21 to 60). If one spouse became obese, the likelihood that the other spouse would become obese increased by 37% (95% CI, 7 to 73). These effects were not seen among neighbors in the immediate geographic location. Persons of the same sex had relatively greater influence on each other than those of the opposite sex. The spread of smoking cessation did not account for the spread of obesity in the network. Network phenomena appear to be relevant to the biologic and behavioral trait of obesity, and obesity appears to spread through social ties. These findings have implications for clinical and public health interventions.


This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author’s clinical recommendations. A 28-year-old woman is referred for advice about the management of recently diagnosed chronic myelogenous leukemia (CML). She was in excellent overall health but was incidentally found to have an elevated white-cell count of 31,000 per cubic millimeter. Bone . . .
IMAGES IN CLINICAL MEDICINE


A 37-year-old man presented to the emergency department with chest pain of 2 days’ duration. The pain was heavy in character, intermittent, and made worse by deep inspiration and lying flat. The man had no shortness of breath and had been actively working as a gardener until the onset of the pain. He was an active smoker, and his father had had a myocardial infarction at the age of 52 years. He did not have hypertension. Auscultation of the precordium was notable for an aortic regurgitant murmur. Electrocardiography showed left ventricular hypertrophy. Chest radiography revealed a widened mediastinum (Panel A). . . .


A 56-year-old woman presented with jaundice and a painless mass in her left supraclavicular fossa that had become progressively enlarged during the preceding 8 weeks. Physical examination revealed a hard lymph node measuring 6 cm by 6 cm in the left supraclavicular fossa (Panel A) and hepatomegaly. Plain radiography of the chest showed multiple nodular opacities in both lungs (Panel B, arrows). Computed tomography of the abdomen revealed multiple lesions in the liver (Panel C, arrows). Endoscopy of the upper gastrointestinal tract showed a fungating mass around the ampulla of Vater. Biopsy specimens from the mass and the supraclavicular lymph . . .


A 25-year-old woman with no clinically significant medical history and with normal coagulation and hematologic studies went bungee jumping from a vertical height of 150 ft (45.7 m). Immediately afterward, she noticed a substantial decrease in vision in her left eye, with a large central scotoma; no other symptoms were noted and there was no pain. On examination, the patient’s right eye was found to have a normal disc and vessels (Panel A, arrowhead) and normal fovea and macula (Panel A, arrow). Examination of the left eye showed a normal disc and vessels (Panel B, arrowhead), but the foveal and . . .


A 60-year-old man presented with progressive swelling of the right side of the scrotum. He reported no history of trauma to this area and no sexually transmitted infections. The alpha-fetoprotein level was elevated at 3100 µg per liter (normal value, <8), and the serum level of the beta subunit of human chorionic gonadotropin was less than 1 IU per liter. Multidetector computed tomography with multiplanar reformation (Panel A) showed a large testicular tumor with lymphangitic spread along the testicular vessels to the associated draining lymph nodes below the renal hilus. Right-sided hydronephrosis is present because of compression of the ureter . . .

VIDEOS IN CLINICAL MEDICINE


Providing positive-pressure ventilation with a face mask and a bag-valve device can be a lifesaving maneuver. Although seemingly simple, the technique requires an understanding of the airway anatomy, the equipment, and the indications. Developing manual skills is necessary to provide adequate face-mask ventilation. While endotracheal intubation is frequently the definitive airway management approach for patients in respiratory failure, it is not always feasible. In these circumstances, ventilating a patient with a face mask can be an invaluable temporizing measure. The purpose of this video is to demonstrate the equipment and technique used to provide positive-pressure . . .

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL


A 38-year-old woman was seen in the Gastrointestinal Cancer Genetics Clinic of this hospital because of a family history of breast and gastric cancer. Approximately 15 months earlier, mild chronic gastrointestinal symptoms, including dyspepsia, heartburn, and midabdominal discomfort, increased in severity and began to occur daily. The symptoms did not resolve with antacid therapy. She had lost approximately 2.3 kg (5 lb) during this time, which she attributed to the stress of caring for her maternal aunt, who was dying of gastric cancer. Seven months before admission, an endoscopic examination of the upper gastrointestinal tract, performed at another hospital, was . . .

Presentation of Case
Dr. Laura Chapman (Pediatrics): A 9-year-old boy with autism was admitted to this hospital because of pain in the hip, refusal to walk, and the recent onset of a rash and gingival swelling. The patient was in his usual state of health until approximately 3 months before admission, when he had an upper respiratory illness with fever; shortly thereafter, he began to have right hip pain, to limp, and to have decreased energy. During the next several weeks, he began to have difficulty climbing stairs, became increasingly irritable, and began moaning in his sleep at night; his appetite decreased, and . . .

**CLINICAL IMPLICATIONS OF BASIC RESEARCH**


Advanced tumors cannot be cured with single drugs. They often are resistant to single agents, and even if they are initially sensitive, their molecular heterogeneity usually guarantees the secondary outgrowth of rare cells that are resistant. In contrast, drug combinations can cure specific types of cancers even at advanced stages; this observation has spurred the development of combination chemotherapy for most types of cancer during the past half century. Examples of effective therapeutic combinations include doxorubicin, bleomycin, vinblastine, and dacarbazine for Hodgkin’s lymphoma and bleomycin, etoposide, and cisplatin for testicular cancer. Most combinations seldom cure disease, however, and their identification . . .

**CLINICAL PRACTICE**


This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations. A 37-year-old man presents for the evaluation of localized swelling and tenderness of the left leg just below the knee. He suspects this lesion developed after a spider bite, although he did not see a spider. Examination of the leg reveals an area of erythema and warmth measuring approximately 5 by 7 cm. At the center of the lesion is a fluctuant . . .

**HEALTH, LAW, ETHICS, AND HUMAN RIGHTS**


J.M. Coetzee’s violent, anti-apartheid Age of Iron, a novel the Wall Street Journal termed “a fierce pageant of modern South Africa,” is written as a letter by a retired classics professor, Mrs. Curren, to her daughter, who lives in the United States. Mrs. Curren is dying of cancer, and her daughter advises her to come to the United States for treatment. She replies, “I can’t afford to die in America. . . . No one can, except Americans.”

Dying of cancer has been considered a “hard death” for at least a century, unproven and even quack remedies have been common, and price . . .