NEWSROUND

Selected reports edited by Janet Fricker

Cytarabine: low dose as effective as high dose in AML

➜ NEJM

Intermediate dose cytarabine was shown to be as effective as high-dose cytarabine in the treatment of acute myeloid leukaemia (AML) with less toxicity, an investigator-led study has concluded.

Cytarabine (ara-C) is one of the cornerstones of treatment for AML. Although high-dose cytarabine is now used routinely for induction and consolidation therapy it has not been compared in studies with intermediate-dose cytarabine, which could result in maximal anti-tumour effects with less toxicity.

In the current study Bob Löwenberg and colleagues, from the Erasmus University Medical Centre (Rotterdam, the Netherlands), compared outcomes for 821 patients with AML (aged 18–60 years) and 39 patients with refractory anaemia with excess blasts (RAEB), who were randomly assigned to high-dose cytarabine (n=429) or intermediate-dose cytarabine (n=431).

The high-dose group received a dose-escalated regimen of 1000 mg/m^2 of cytarabine every 12 hours in cycle 1 and 2000 mg/m^2 twice daily in cycle 2. The intermediate-dose group, received cytarabine at a dose of 200 mg/m^2 given by continuous intravenous infusion for 24 hours during cycle 1 of induction therapy and 1000 mg/m^2 by infusion for 3 hours twice daily during cycle 2 of induction therapy. For the third cycle patients with a complete response received consolidation therapy with chemotherapy (mitoxantrone–etoposide) or underwent autologous or allogeneic stem-cell transplantation.

Results show that, at a median follow-up of five years, complete remission rates were 80% for the intermediate-dose group versus 82% for the high-dose group (HR=1.14, 95%CI 0.81–1.60; P=0.45).

In the first three months there were 72 deaths in the high-dose group versus 52 in the intermediate-dose group (HR=1.41; P=0.057). However, at five years there were no significant differences between the intermediate-dose group and high-dose group in the rate of probability of relapse, event-free survival or overall survival. High-dose cytarabine provided no clear advantage for any prognostic subgroup.

After the first cycle, 61% of patients in the high-dose cytarabine group suffered grade 3 to 4 adverse events versus 51% in the intermediate-dose group (P=0.005). Specifically, skin reactions and gastrointestinal and ocular toxic effects were noted. Additionally in cycle 2, more patients in the high-dose group suffered prolonged hospitalisation and delayed neutrophil recovery, and in cycles 2 and 3 more patients in the high-dose group suffered delayed platelet recovery.

"The results suggest that the anti-

leukaemic effects of cytarabine may reach a maximum at doses well below the maximum tolerated dose," conclude the authors, adding "... the high-dose cytarabine regimen resulted in considerable toxic effects, was significantly more myelosuppressive, and required more platelet transfusions and prolonged hospitalization. Myelosuppression of high-dose cytarabine appears cumulative and is carried over to post remission chemotherapy."

■ B Löwenberg, T Pabst, E Vellenga et al. Cytarabine dose for acute myeloid leukemia. *NEJM* 17 March 2011, 364:1027–1036

Eribulin delivers overall survival benefit in metastatic breast cancer

→ The Lancet

Eribulin produced a significant improvement in overall survival in women with heavily pre-treated metastatic breast cancer when compared to treatments selected by doctors, the EMBRACE study has reported.

It is widely recognised that a great need exists for new treatments to improve overall survival in women with advanced or recurrent metastatic breast cancer, particularly those with heavily pre-treated disease. Eribulin mesilate is a non-taxane microtubule dynamics inhibitor that is a structurally modified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge Halichondria okadai.

In the phase III EMBRACE trial, led by Chris Twelves from the University of Leeds in the UK, 762 women with metastatic breast cancer who had received a median of four previous chemotherapy regimens from 135 centres in 19 countries were randomly allocated, in a 2:1 ratio, between November 2006 and November 2008, to treatment with eribulin (*n*=508) or to the treatment of physician's choice (*n*=254). The treatment of physician's choice (TPC) arm represented a mix of agents (both approved and non-approved for metastatic breast cancer) intended to mirror clinical practice at the time of the study. In the TPC arm 96% received chemotherapy, with vinorelbine, gemcitabine and capecitabine being the most frequently used agents. Patients and investigators were not masked to treatment allocation.

Results show that overall survival was 13.1 months in women assigned to eribulin versus 10.6 months in women assigned to TPC (HR=0.81, 95%CI 0.66–0.99; *P*=0.041). Furthermore, median progression-free survival was 3.7 months with eribulin versus 2.2 months with TPC (HR=0.87, 95%CI 0.71–1.05; *P*=0.137).

Asthaenia or fatigue occurred in 54% of patients on eribulin versus 40% on TPC, and neutropenia occurred in 52% of patients receiving eribulin versus 30% receiving TPC. Peripheral neuropathy was the most common adverse event, leading to discontinuation from eribulin in 5% of patients.

"This ... study establishes a potential new standard treatment for women with heavily pre-treated metastatic breast cancer, for whom there was previously no chemotherapy treatment with proven survival benefit," write the authors, adding that on the basis of the results, eribulin has received approval in the USA for patients who have received at least two chemotherapeutic regimens for the treatment of metastatic breast cancer, with previous treatments including an anthracycline and a taxane.

Eribulin, they add, has a manageable profile of toxic effects, short infusion times, and is easy to administer with no requirement for premedication to prevent hypersensitivity. Further evaluation of eribulin earlier in the natural history of breast cancer is now warranted.

■ J Cortes, J O'Shaughnessy, D Loesch, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Original text. *Lancet* 12 March 2011, 377:914–923

Small proportion of second cancers related to radiotherapy

→ Lancet Oncology

Around 8% of second cancers that develop in adult cancer survivors are related to radiotherapy, an analysis of the US Surveillance, Epidemiology and End Results (SEER) cancer registries has found. The majority of second cancers, said the authors, are attributable to lifestyle or genetics.

Radiotherapy reduces the risk of cancer recurrence, promotes tumour control, and improves survival. However, with improvements in survival, the long-term risks from radiotherapy, including the risk of developing a second cancer, have become more important.

In the current study Amy Berrington de Gonzalez and colleagues, from the National Cancer Institute (Bethesda, Maryland), undertook a comprehensive and systematic analysis of data recorded in the US SEER cancer registries on 15 solid cancer sites in adults who had been routinely treated with radiotherapy. Patients were aged 20 years or older and had been diagnosed with their first primary invasive solid cancer between January 1973 and December 2002. Due to the five-year lag between radiation exposure and solid-cancer induction, investigators excluded patients who survived less than five years from treatment.

Relative risks (RRs) for a second cancer in patients treated with radiotherapy versus patients not treated with radiotherapy were estimated using Poisson regression analysis adjusted for age, stage, and other potential confounders.

Altogether 647,672 adult cancer patients in the cohort survived for five years or longer and were followed up for a mean of 12 years. The proportion of patients who received radiotherapy as part of their initial cancer treatment varied from 23% for non-small-cell lung cancer to 79% for testicular seminomas.

Results showed that the attributable risk of a second cancer to radiotherapy was 5%

for cancers of the oral cavity/pharynx, 12% for the salivary glands, 7% for the rectum, 10% for the anus, 5% for the larynx, 6% for the lung, 15% for soft tissue, 5% for female breast, 17% for the cervix, 9% for the endometrium, 10% for the prostate, 24% for the testes, 4% for the eye/orbit, 9% for the brain and 7% for the thyroid. Overall the attributable risk was 8%.

In general, the investigators found that relative risk was highest for organs that received greater than 5 Gy, decreased with increasing age at diagnosis, and increased with time since diagnosis.

"These findings can be used by physicians and patients to put the risk of radiation-related cancer into perspective when compared with the probable benefits of the treatment," write the authors, adding that studies are now needed of secondary cancer risks related to newer radiotherapy treatments.

The strengths of the study include its systematic approach, large sample size and long-term follow-up, with the main limitation being lack of treatment randomisation, providing a potential for confounding factors.

■ A Berrington de Gonzalez, RE Curtis, SF Kry, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. *Lancet Oncol* April 2011, 12:353–360

Colonic stenting delivers no advantages over emergency surgery in malignant colonic obstructions

→ Lancet Oncology

Colonic stenting offers no decisive advantage over emergency surgery in patients with acute malignant colonic obstruction, concluded a Dutch study.

Around 7%–29% of patients with colorectal cancer present with bowel obstructions that require emergency surgery to restore luminal patency (unblock the passage). Emergency surgery is associated with mortality rates of 15%–34% and morbidity rates of 32%–64%. In the early 1990s colonic stenting was introduced to restore luminal patency in patients with malignant obstruction on the left side of the colon, with uncontrolled studies suggesting that stent placement before elective surgery decreases mortality, morbidity and the number of colostomies. Additional advantages that have been suggested for the temporary procedure are that it enabled accurate tumour staging and prevented the need for surgery in patients found to have disseminated disease.

Jeanin van Hooft and colleagues from the University of Amsterdam, in the Netherlands, set out to establish whether colonic stenting delivers better health outcomes than emergency surgery. Between March 2007 and August 2009, 98 patients with acute obstructive left-sided colorectal cancer from 25 hospitals in the Netherlands were randomly assigned in a 1:1 ratio to colonic stenting as a bridge to elective surgery (n=47) or emergency surgery (n=51).

At six months investigators found no difference between treatment groups in global health status (assessed with the QL2 subscale of the EORTC quality-of-life questionnaire). Mean global health status was 63.0 (SD 23.8) in the colonic stenting group versus 61.4 (SD 21.9) in the emergency surgery group (P=0.36). Furthermore, no difference was recorded for 30-day mortality (P=0.89), overall mortality (P=0.84), morbidity (P=0.43) and stoma rates at latest follow-up (P=0.35). The most common serious adverse events were abscess (three in the colonic stenting group versus four in the emergency surgery group), perforations (six versus none), and anastomotic leakage (five versus one).

"In this multicentre randomised trial, colonic stenting or emergency surgery did not have any distinct benefits for global health status, mortality, morbidity, other quality-of-life dimensions, and stoma rates," conclude the authors, adding that further studies are needed to establish whether specific groups of patients might have experienced greater benefit in either group.

While colonic stenting can be used as an alternative to emergency surgery, write the authors, caution should be exercised due to concerns over overt and silent perforations, which are more likely to occur with stents and might result in distant seeding of malignant cells.

In an accompanying commentary, Louis Wong Kee Song and Todd Baron from the Mayo Clinic (Rochester, Minnesota), wrote that until improvements in colonic stent design are addressed, endoscopic preoperative colonic stenting should be undertaken in selected centres and in selected patients deemed most likely to benefit.

■ J Evan Hooft, WA Bemelman, B Oldenburg et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. *Lancet Oncol* April 2011, 12:344–352

■ L Wong Kee Song, T Baron. Stenting for acute malignant colonic obstruction: a bridge to nowhere? *ibid*, pp 314–315

Denosumab represents treatment option for bone metastases in prostate cancer

→ The Lancet

Denosumab proved better than zoledronic acid, the standard of care, in preventing skeletal-related events in men with bone metastases from castration-resistant prostate cancer, an international phase III study has found.

Bone metastases are a major burden for men with advanced prostate cancer. Histological findings, together with analysis of bone turnover markers, suggest that excess osteoclastic activity is responsible for bone

destruction in metastatic disease. Denosumab is the first fully human monoclonal antibody developed to specifically target RANK ligand, a key mediator of osteoclast formation, function and survival. In studies denosumab has been shown to reduce bone resorption, tumour-induced bone destruction and skeletal-related events.

In the current study, led by Karim Fizazi from the Institut Gustave Roussy (Villejuif, France), investigators from 342 centres in 39 countries randomised 1904 men with castration-resistant prostate cancer and no previous exposure to intravenous bisphosphonate in a 1:1 ratio to receive 120 mg subcutaneous denosumab plus intravenous placebo (*n*=950), or 4 mg intravenous zoledronic acid plus subcutaneous placebo (*n*=951), every four weeks.

Results show that the median time to first on-study skeletal-related event was 20.7 months with denosumab versus 17.1 months with zoledronic acid (HR=0.82, 95%CI 0.71–0.95; *P*=0.0002 for non-inferiority; *P*=0.008 for superiority). Adverse events were recorded in 97% of patients on denosumab versus 97% on zoledronic acid, and serious adverse events were recorded in 63% of patients on denosumab versus 60% on zoledronic acid. The only differences were raised rates of hypocalcaemia (13%) and osteonecrosis (2%) in the denosumab group.

"We have shown that denosumab is better than the established therapy, zoledronic acid, for the delay or prevention of skeletal-related events in patients with advanced prostate cancer," write the authors, adding that two limitations of the study were that the double-dummy design did not allow them to objectively measure the benefits of subcutaneous versus intravenous administration, and that the protocol prevented them from assessing treatment benefits in patients with severe renal dysfunction at baseline.

In an accompanying commentary, Jeanny Aragon-Ching from George Washington University Medical School, describes the advantages of using denosumab over zoledronic acid.

"Denosumab is easier to give (subcutaneous) than is zoledronic acid, allowing for shorter visit times and applicability in various physicians' office settings by removing the need for an infusion clinic. Furthermore, denosumab reduces the need for management of acute phase reactions and renal monitoring or dose adjustments, although caution should be exercised with patients who have poor baseline kidney function."

Further quality-of-life and pain response data, she adds, would have been helpful, since fatigue, bone pain and asthenia were reported almost equally in both groups.

■ K Fizazi, M Carducci, M Smith et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*, 5 March 2011, 377:813–822

■ J Aragon-Ching. Unravelling the role of denosumab in prostate cancer. *ibid* pp 785–786

Success of sperm retrieval depends on chemotherapy used

➜ Journal of Clinical Oncology

Sperm retrieval using testicular sperm extraction (TESE) coupled with intracytoplasmic sperm injection (ICSI) resulted in sperm retrieval in 37% of patients who had undergone previous chemotherapy, reported a US study. The study – representing the largest series of postchemotherapy microdissection TESE–ICSI yet – found that the success of fertility techniques was related to the type of cancer that patients had originally been diagnosed with.

Advances in chemotherapy have led to greater longevity for young men, with the preservation of fertility and paternity becoming increasingly important as a quality of life issue. It has been estimated that up to two-thirds of men undergoing chemotherapy remain persistently azoospermic (no measurable level of sperm) after treatment. While men rendered persistently azoospermic have traditionally been considered sterile and referred for adoption or use of donor sperm, there is growing recognition that fertility can be salvaged with TESE–ICSI.

In the current study Peter Schlegel and colleagues, from the New York Presbyterian Hospital (US), retrospectively identified 73 patients with persistent postchemotherapy azoospermia from a series of testicular sperm extraction procedures performed between June 1995 and December 2009 by a single surgeon in 892 patients. The results show that spermatozoa were retrieved in 37% of patients (27 of 73), with an overall sperm retrieval rate of 42.9% (36 of 84). This resulted in a 57.1% fertilisation rate per injected oocyte and an overall live birth rate of 42%. Altogether there were 15 deliveries involving a total of 20 children.

When the sperm retrieval rate was stratified according to indications for chemotherapy, the highest retrieval rates were seen in patients with testicular cancer (85.7%), followed by neuroblastoma (50%), leukaemia (50%), non-Hodgkin's lymphoma (36.4%), Hodgkin's lymphoma (25.9%) and sarcoma (14.3%). "Sarcoma patients tended to have the lowest sperm retrieval rate due to high rates of exposure and higher doses of alkylating agents," write the authors.

With the mean time elapse since chemotherapy of 18.6 years, this led the authors to question whether sperm retrieval closer to the time of chemotherapy might have led to a higher success rate.

"Our data demonstrates that many men with long-term azoospermia after chemotherapy can still have their fertility salvaged with the use of assisted reproductive techniques," conclude the authors.

■ W Hsiao, PJ Stahl. EC Osterberg et al. Successful treatment of post chemotherapy azoospermia with microsurgical testicular sperm extraction: the Weill Cornell experience. *JCO* doi: 10.1200/JCO.2010.33.7808, published online 14 March 2011