NEWSROUND

Selected reports edited by Janet Fricker

AML: high-dose daunorubicin impacts on survival

➜ New England Journal of Medicine

Giving high-dose daunorubicin to patients with acute myeloid leukaemia (AML) during the induction phase improves the response to chemotherapy, according to the results of two trials published in the same issue of the *NEJM*. In an accompanying editorial, Hervé Dombret and Claude Gardin, from the University of Paris, comment that, taken together, the two trials – one US and the other European – "establish a new standard of care for AML for some patients."

In the US study (involving patients aged 17 to 60) high-dose daunorubicin resulted in higher rates of complete remission and improved overall survival. While the European study (involving patients aged 60 to 83) showed a statistically significant improvement in complete response, only the subgroup of patients aged between 60 and 65 actually demonstrated an improvement in overall survival.

For more than 20 years, the standard induction therapy for attaining complete remission in AML has been an anthracycline – daunorubicin mostly – at a daily dose of 45–60 mg/m^2 of body surface area for three days, in combination with cytarabine for seven days. Neither adding other drugs during the induction phase nor increasing the dose of cytarabine has resulted in improved survival. The current studies from the Eastern Cooperative Oncology Group (ECOG) in the US and a collaborative group of European investigators from the Netherlands, Belgium, Germany and Switzerland, assessed the benefits of doubling the induction phase dose of daunorubicin.

In the ECOG study, led by Hugo Fernandez, 657 patients with untreated AML, aged between 17 and 60, were randomised to receive daunorubicin at 45 or 90 mg/m^2 once daily for three days, plus cytarabine dosed at 100 mg/m^2 daily, administered by continuous infusion for seven days. Results showed that the rate of complete remission was 70.6% in the high-dose group versus 57.3% with the low-dose group (P<0.001), and the overall median survival was 23.7 months for the high-dose group compared to 15.7 months for the low-dose group (P=0.003).

The US authors commented that, while "intensifying induction therapy with a high daily dose of anthracycline plus intensive consolidation therapy resulted in a high complete-remission rate and prolonged overall survival" in patients with AML, no benefits occurred in patients over the age of 50 or in those with unfavourable cytogenetic profiles (*FLT3*-ITD mutations or *MLL*-PTD mutations). The authors speculate that the presence of *MDR1* gene overexpression, which is more frequent in older patients with AML and causes efflux of daunorubicin from the cell, may have contributed to the poor responses in older age groups.

The European investigators, led by Bob Löwenberg from the Erasmus University Medical Centre, in Rotterdam, the Netherlands, undertook a similar approach, randomising 813 patients, aged 60 to 83, with newly diagnosed AML or high-risk refractory anaemia, to the conventional dose of

45 mg/m² daunorubicin (n=411) or to the escalated dose of 90 mg/m² (n=402). Treatment was in addition to cytarabine.

Results show the complete remission rate was 64% in the group receiving escalated daunorubicin, compared to 54% in the group receiving the conventional dose (P=0.002). While survival endpoints in the two groups did not differ significantly overall, an exploratory *post hoc* analysis showed patients in the escalated treatment group in the 60- to 65-years age group achieved 38% overall survival compared to 23% for patients in the conventional group.

"In our study, it is apparent that the subgroup of patients who were 60 to 65 years of age benefited the most from intensified doses of daunorubicin," write the authors.

Neither trial saw an increase in serious side-effects from the higher dose of daunorubicin. "The lack of an increase in toxic effects and the benefit in overall survival strongly argue for incorporating high-dose daunorubicin into the initial treatment of younger patients with AML, at least those with favorable- and intermediate-risk cytogenetic profiles," write Dombret and Gardin in the accompanying editorial.

For older patients, they add, idarubicin might offer an alternative to daunorubicin, since a recent study showed no difference in outcome between high-dose daunorubicin and standard-dose idarubicin. "The main issues now are how to improve the selection of patients who should be offered intensive therapy and how to develop new approaches to increase survival in this age group," they conclude.

- Anthracycline dose intensification in acute myeloid leukemia. HF Fernandez, Z Sun, X Yao et al. *NEJM* 24 September 2009, 361:1249–1259
- Highdose daunorubicin in older patients with acute myeloid leukemia. B Löwenberg, GJ Ossenkoppele, W van Putten et al. *ibid*, pp 1235–1248
- An old AML drug revisited [editorial]. H Dombret and C Gardin. *ibid*, pp 1301–1303

Colorectal screening is cost effective

➔ JNCI

Colorectal cancer screening both reduces the incidence of cancer and leads to patients undergoing cheaper methods of treatment, a Dutch simulation study has concluded.

Colorectal cancer is considered to be particularly well-suited for screening, due to its long preclinical phase and favourable survival for patients whose disease is detected at an early stage. Indeed, studies have shown that screening reduces mortality by 15%–33%. However, on the downside, colorectal cancer screening requires considerable net investment by governments or insurance companies.

In the current study, Iris Lansdorp-Vogelaar and colleagues, from the Erasmus Medical Centre in Rotterdam, the Netherlands, reasoned that if screening could be shown to save costs, governments and insurance companies might feel more inclined to invest in programmes. The team therefore decided to examine whether colorectal cancer screening would become cost saving with the introduction of new and expensive chemotherapies.

To explore how increased treatment costs would influence the cost savings of various screening methods, the researchers used a validated microsimulation model, called the MISCAN-Colon model, which stimulates the relevant biographies of a large population of fictitious individuals from birth to death, first in the absence of screening and subsequently with changes that are predicted to occur under the implementation of a screening programme.

The team assessed screening with guaiac faecal occult blood testing (FOBT) with Hemoccult II, annual immunochemical FOBT, sigmoidoscopy every five years, colonoscopy every 10 years, and the combination of sigmoidoscopy every five years and annual guaiac FOBT. For their part, chemotherapy treatment options were classified as past (1990–1994), present (1998–2003) and near future (using recent clinical trial results).

The analyses were undertaken from the perspective of the healthcare system for a cohort of 10 million 50-year-old individuals from the US who were at average risk of colorectal cancer and screened with 100% adherence from age 50 to 80 years and followed up until death. The primary assumption made in the study was that the costs of screening would remain flat, whereas treatment costs would increase over time.

Results showed that the lifetime average treatment savings for the entire population were larger than the lifetime average screening costs for all methods except for colonoscopy, as follows:

- Guiaic FOBT with Hemoccult II ($1,398 average treatment savings vs $859 lifetime average screening costs)
- Immunochemical FOBT ($1,756 average treatment savings vs $1,565 lifetime average screening costs)
- Sigmoidoscopy ($1,706 average treatment savings vs $1,575 lifetime average screening costs)
- Sigmoidoscopy combined with Hemoccult II ($1,931 average treatment savings vs $1,878 average screening costs)

Although colonoscopy did not produce an overall cost saving, the total net costs decreased from $1,317 to $296 per patient.

The drawback to implementation of screening programmes, write the authors, is that there is a lead time before screening starts to produce cost savings. Time-to-cost-saving was shortest for a screening programme with Hemoccult II (26 years), followed by immunochemical FOBT (37 years), sigmoidoscopy (40 years) and the combination of Hemoccult II and sigmoidoscopy (47 years).

Insurance companies, comment the authors, may therefore be reluctant to implement screening programmes, when many of the beneficiaries do not stay in the scheme beyond five years, and indeed, in the US, most of the benefits will accrue when

patients have passed into the Medicare programme. For this reason, they suggest, it might make good sense for Medicare to help pay for establishing screening programmes for individuals younger than 65.

"Given the potential cost savings from screening, screening not only is desirable from the perspective of governments and insurance companies to reduce colorectal cancer incidence and mortality, but also will help to contain the increasing costs for the management of colorectal cancer," conclude the authors, adding that although the results are based on the US they are just as applicable to the European situation.

The authors acknowledged that the study has several limitations. One of these is that treatment costs may have been underestimated because therapies other than chemotherapy (such as radiotherapy for rectal cancer and extensive surgery for metastatic disease) were not included in the analysis. Another limitation is the assumption made that all patients with stage III and IV disease would receive new chemotherapies, whereas in real life practice, elderly patients with comorbidities may not.

■ Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. I Lansdorp-Vogelaar, M van Ballegooijen, AG Zauber et al. *JNCI* 21 October 2009, 101:1412–1422

EGFR mutations identify NSCLC candidates for erlotinib

➔ New England Journal of Medicine

Screening lung cancer patients for the presence of epidermal growth factor receptor (EGFR) gene mutations can help to identify the subgroups who will benefit most from treatment with the tyrosine kinase inhibitor erlotinib, a Spanish study has found.

In retrospective studies, EGFR mutations have been found to be independent predictors of response, progression-free survival and overall survival in patients with non-small-cell lung cancer treated with gefitinib. In the current study, between April 2005 and November 2008, Rafael Rosell and colleagues from the Catalan Institute of Oncology in Barcelona, Spain, undertook a prospective study screening for EGFR mutations in 2105 patients with advanced non-small-cell lung cancer from 129 centres throughout Spain. Patients found to have mutations were then considered for erlotinib treatment at a dose of 150 mg daily until disease progression or intolerable adverse effects, with the investigators evaluating the association between EGFR mutations and outcomes.

The investigators found that EGFR mutations were present in 16.6% of the patients screened, and occurred more frequently in patients with adenocarcinomas (80.9%), women (69.7%), and those who had never been smokers (66.6%) ($P<0.001$ for all comparisons). The mutations were found to be deletions in exon 19 in 62.2% of cases and L858R in 37.8%.

Overall for the 217 patients receiving erlotinib (113 as first-line therapy and 104 as second- or third-line therapy), the median progression-free survival was 14 months and median overall survival was 27 months. The overall rate of complete or partial response to erlotinib was 70.6%. The results, say the authors, demonstrate an improvement over findings in patients with lung cancer reported previously. In patients who do not have this mutation, chemotherapy normally yields a 30% response, a five-month progression-free survival, and a 12-month median survival.

The most common adverse events were skin rashes (in 69.6% of patients – $n=151$) and diarrhoea in 43.8% of patients – $n=95$). Most events were grade 1 or 2 in severity.

In the multivariate analysis of overall survival, an ECOG performance status of 1, male sex, the presence of the L858R mutation and the diagnosis of bronchioloalveolar adenocarcinoma were associated with poor prognosis.

"In conclusion," write the authors, "screening for EGFR mutations is warranted in women with lung cancer, in those who have never smoked, and in those with non-squamous tumors. Large-scale screening of patients for EGFR mutations, with subsequent customization of erlotinib, is feasible and improves the outcome." They add that the results highlight the idea that EGFR lung cancer is a distinct class of non-small-cell lung cancer.

■ Screening for epidermal growth factor receptor mutations in lung cancer. R Rosell, T Moran, C Queralt et al. *NEJM* 19 August 2009, 361:958–967

New drug reduces fracture incidence in androgen deprivation therapy

➔ New England Journal of Medicine

Denosumab is associated with increased bone mineral density at all sites and a reduction in the incidence of new vertebral fractures in men receiving androgen deprivation therapy for nonmetastatic prostate cancer, a phase III study has found.

While androgen-deprivation therapy is well established for treating prostate cancer, it is also associated with bone loss and an increased risk of fractures. Although several drugs, including bisphosphonates and selective oestrogen-receptor modulators, have been shown to prevent bone loss associated with androgen deprivation therapy, published trial results showing an effect on fracture prevention are lacking. Furthermore, no approved therapy is currently indicated for reducing the risk of fracture in men receiving androgen-deprivation therapy for prostate cancer.

The HALT Prostate Cancer Study Group, led by Matthew Smith from the Massa-

chusetts General Hospital Cancer Center in Boston, Massachusetts, investigated the effects of denosumab – a fully human monoclonal antibody – against a receptor activator of nuclear factor-κB ligand, on bone mineral density and fractures in men receiving androgen-deprivation therapy for non-metastatic prostate cancer.

In the double-blind, multicentre study, investigators randomly assigned patients from 156 study centres in North America and Europe to receive denosumab at a dose of 60 mg subcutaneously (n=734) or placebo (n=734) every six months. The primary endpoint of the study was the percentage change in bone mineral density at the lumbar spine at 24 months, while secondary endpoints included changes in bone mineral densities at the femoral neck and total hip at 24 months and at all three sites at 36 months, as well as incidence of new vertebral fractures.

Results show at 24 months the bone mineral density of the lumbar spine had increased by 5.6% for those in the denosumab group compared to a loss of 1% for those in the placebo group (P<0.001). Furthermore, patients who received denosumab had an incidence of 1.5% new vertebral fractures at 36 months compared to 3.9% for patients taking placebo (relative risk 0.38, 95% CI 0.19–0.78, P=0.006). Additionally, denosumab therapy was associated with significant increases in bone mineral density at the total hip, femoral neck and distal third of the radius at all time points. Rates of adverse events were similar between the two groups.

"In conclusion, twice-yearly administration of denosumab was associated with increases in bone mineral density at all skeletal sites and reduction in vertebral fractures in men receiving androgen deprivation therapy for prostate cancer," write the authors, adding that the beneficial effects appeared robust as they were found as early as one month after therapy began and were sustained for three years.

In an accompanying *NEJM* editorial, Sundeep Khosla from the Mayo Clinic, in Rochester, Minnesota, commented that there have yet to be any head-to-head trials comparing denosumab with other osteoporosis drugs. "Nonetheless, the magnitude of risk reduction for vertebral fractures with denosumab appears to be similar to that reported for intravenous zoledronic acid or teriparatide 5, and perhaps somewhat greater than that seen with oral bisphosphonates. Risk reductions for nonvertebral fractures appear to be in the same range for all these agents. Thus, denosumab seems at least as efficacious as the best of the currently approved alternatives."

With regard to long-term safety, he added, although denosumab did not appear to increase the infection rate, its potential to depress immune function remained an issue. Cost might also become relevant, he added, if denosumab turns out to be priced much higher than zoledronic acid, the bisphosphonate drug viewed as its most direct competitor. "Given the relatively marginal clinical differences between these two drugs, a higher cost of denosumab would considerably limit its use," he wrote.

■ Denosumab in men receiving androgen-deprivation therapy for prostate cancer. MR Smith, B Egerdie, N Hernández Toriz et al. *NEJM* 20 August 2009, 361:745–755

■ Increasing options for the treatment of osteoporosis [editorial]. S Khosla. *ibid* pp 818–820

Assessing the needs of patients with advanced, incurable cancer

➜ British Journal of Cancer

Patients with advanced, incurable cancer have the highest levels of unmet needs in the areas of psychological support and medical communication/information, concludes an Australian questionnaire study. The results, say the authors, offer the potential to guide the development of future interventions.

Limited research has been undertaken to investigate the specific needs of patients with advanced incurable cancer, creating uncertainty among healthcare professionals as to what areas require addressing when caring for this vulnerable group. Uncertainty has been exacerbated by studies failing to distinguish between 'needs' and 'problems'. Although patients may perceive they have a problem, they may decide to endure and not register it as a need. The hair loss resulting from chemotherapy, for example, may be a problem, but patients are prepared to accept it in an effort to prolong life, and hence perceive no need for help.

In the current study, Rob Sanson-Fisher and colleagues, from the University of Newcastle in New South Wales, Australia, set out to examine the prevalence of unmet needs among a sample of patients with advanced, incurable cancer who were not receiving formal palliative care. Forty-four medical specialists from two regions in New South Wales identified 418 patients with advanced, incurable cancer, who were estimated to have a life expectancy of less than two years, but more than three months, and were not receiving formal palliative care. Altogether 246 patients (59%) consented to complete the Needs Assessment for Advanced Cancer Patients' questionnaire, which assessed patients' perceived needs – psychological, daily living, medical communications and information, symptom-related, social, spiritual and financial.

For moderate/high levels of need, the results show that 39%–40% of patients felt they had psychological or emotional needs, 31%–35% had medical communication/ information needs, 10%–15% had financial needs and 11%–15% had spiritual needs.

Patients' specific needs were highest in

dealing with lack of energy and tiredness (experienced by 41%), coping with fears about the cancer spreading (40%) and coping with the frustrations of not being able to do the things that they used to do (40%). With regard to perceptions of life expectancy, only 5% of the patients who the clinicians thought had a life expectancy of less than two years shared this perception. Furthermore, 30% of patients reported that their doctor had not discussed life expectancy with them.

The research, say the authors, shows that 95% of patients with advanced, incurable cancer have some level of perceived need for help, and that they experience moderate or high needs across a variety of domains. "These data suggest that the existing health-care system is not meeting the needs of these patients," they conclude, noting also that the study illustrates the often ambiguous nature of a patient's understanding of their own prognosis and diagnosis, and that the level of information needs varies between patients. "This finding suggests the desirability for physicians to explicitly assess what each individual patient knows and would like to be told about their condition so that their information needs might be successfully met," they write.

■ The needs of patients with advanced, incurable cancer. K Rainbird, J Perkins, R Sanson-Fisher et al. *Br J Cancer* 25 August 2009, 101:759–764

BIG 1-98: sequential treatment confers no additional benefits

➜ New England Journal of Medicine

Sequential therapy with an aromatase inhibitor (AI) followed by tamoxifen (or vice versa) delivers no improvements in disease-free survival compared to monotherapy with an AI in postmenopausal women with receptor-positive early breast cancer, concludes the latest study from the BIG 1-98 collaborative group.

Initial results from the BIG 1-98 trial showed that the AI letrozole given alone, as compared with tamoxifen given alone, reduced the risk of recurrent disease, especially at distant sites. What has remained unknown is whether sequential treatment with tamoxifen and letrozole is superior to letrozole therapy alone. In the current study, the BIG 1-98 investigators set out to compare letrozole monotherapy with sequential treatment of tamoxifen and letrozole; and in addition investigated whether letrozole monotherapy prolongs overall survival compared with tamoxifen monotherapy.

Between April 1999 and May 2003, 6182 women were randomly assigned to one of four treatment arms: tamoxifen only for five years (n=1548), letrozole only for five years (n=1546), letrozole for two years followed by tamoxifen for three years (n=1540), or tamoxifen for two years followed by letrozole for three years (n=1548). Furthermore, an updated monotherapy analysis was undertaken including 4922 women randomly assigned to letrozole monotherapy or tamoxifen monotherapy as part of either the two- or four-group randomisation options.

The primary endpoint was disease-free survival, defined as the time from randomisation to either recurrence of the disease at a local, regional or distant site; a new invasive cancer in the contralateral breast; any second (non-breast cancer); or death without a previous cancer event. Clinical assessments were performed at baseline, then every six months for the first five years, and at yearly intervals thereafter.

Results show that, at a median follow-up of 71 months, disease-free survival was not significantly improved with either of the sequential treatment approaches compared with letrozole alone. The hazard ratio (HR) for tamoxifen followed by letrozole was 1.05 (95% CI 0.84–1.32); while the HR for letrozole followed by tamoxifen was 0.96 (95% CI 0.76–1.21).

For the updated intention-to-treat analysis, comparing letrozole monotherapy with tamoxifen monotherapy showed that 509 primary endpoint events occurred in the letrozole group, versus 565 events in the tamoxifen group (P=0.03). Furthermore, the time to distant recurrence also differed in favour of the letrozole group (P=0.05). The five-year overall survival was 91.8% in the letrozole group versus 90.9% in the tamoxifen group (HR 0.87; 95% CI 0.75–1.02; P=0.08).

"The present analysis shows that treatment with letrozole for 2 years followed by tamoxifen yielded outcomes similar to those seen with letrozole monotherapy," write the authors, adding that it is possible that part of the beneficial effect in the group given letrozole followed by tamoxifen may have resulted from carryover benefits from the initial letrozole therapy, similar to that observed after the cessation of anastrozole in the ATAC study.

The limitations of the updated intention to treat analysis, add the authors, include the selective crossover to letrozole among women initially assigned to tamoxifen monotherapy and the inability, after a median follow-up period of six years, to assess the influence of a potential carryover effect of letrozole on the results.

"Our belief that this result underestimates the survival benefit that would have accrued if there had been no crossover to letrozole is based on evidence from independent trials that have shown a survival benefit from switching to an aromatase inhibitor after initial treatment with tamoxifen," write the authors.

■ Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. The BIG 1-98 collaborative group. *NEJM* 20 August 2009, 361:766-776