newsround

Selected reports edited by Janet Fricker

ABVD less effective and more toxic in older patients

■ Journal of Clinical Oncology

In patients aged 60 years or older with Hodgkin lymphoma (HL), four cycles of ABVD is associated with substantial toxicity, resulting in grade 3–4 toxicities in more than two-thirds of them, a German study has found. Older patients are also more likely to experience dose reduction, treatment delays and treatment-related mortality.

Approximately 20% of all patients with Hodgkin lymphoma are aged over 60, and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy is regarded as standard of care for these patients. Little is known, however, about the feasibility and efficacy of ABVD in this age group.

In the current study, Peter Borchmann and colleagues from the University Hospital of Cologne, Germany, compared the feasibility and efficacy of four cycles of ABVD in patients aged 60 to 75 years with early-stage Hodgkin lymphoma, who were treated within the German Hodgkin Study Group (GHSG) HD10 and HD11 trials, with that of younger patients (defined as under 60 years).

HD10 randomly assigned patients with early-stage, favourable Hodgkin lymphoma to two or four cycles of ABVD and then 20 Gy or 30 Gy of involved-field radiotherapy (IFRT); while HD11 randomly assigned patients with early-stage, unfavourable/intermediate disease to four cycles of ABVD versus BEACOPP and 20 Gy versus 30 Gy IFRT.

To achieve a more 'homogeneous' group, the authors combined and analyzed patients from both studies who had received four cycles of ABVD followed by either 30 Gy or 20 Gy IFRT.

In total, 1299 patients received four cycles of ABVD; of these, 117 were 60 years or older (median, 65 years). In 16 of these older patients (14%), treatment was not administered according to the protocol, mainly due to excessive toxicity. The mean treatment delay was 2.2 weeks for older patients, versus 1.2 weeks in younger patients.

Of the older patients, 59% achieved a relative dose-intensity of at least 80%, compared with 85% of younger patients.

WHO grade 3 and 4 toxicities during chemotherapy (including leucopoenia, nausea, and infection) were documented in 68% of older patients versus 50% of the younger group. Grade 4 toxicities were seen in 18% versus 7% ($P<0.001$), and treatment-related mortality was 5% versus 0.3% ($P<0.001$).

In terms of efficacy, the complete remission rate was 89% in the older group compared to 96% in the younger group ($P=0.006$), five-year progression-free survival was 75% versus 81% in the younger group, and overall survival at five years was 90% in the older groups versus 97% in the younger group.

"These findings challenge ABVD as standard treatment and underscore the necessity to develop treatment strategies suited for the specific needs of older patients with HL," write the authors.

In an accompanying commentary, Andrew Evens, from the University of Massachusetts Medical School, Worcester, Massachusetts, and Fangxin Hong, from the Dana-Farber Cancer Institute, Boston, Massachusetts, write that the first step to improve outcomes should be to design clinical trials specifically for older patients. "Multicenter collaborations that integrate novel agents and incorporate formal assessments of functional status to tailor therapy on a patient-specific basis will be critical to the successful study of and improved outcomes for older patients with HL," they write.

■ B Böll, H Görgen, M Fuchs. ABVD in older patients with early-stage Hodgkin lymphoma treated within the German Hodgkin Study Group HD10 and HD11 Trials. *JCO* 20 April 2013, 31:1522–29

■ A Evens, F Hong. How can outcomes be improved for older patients with Hodgkin lymphoma? *ibid* pp1502–05

Axillary node dissection can be avoided in patients with limited sentinel node involvement

■ Lancet Oncology

The International Breast Cancer Study Group (IBCSG) 23-01 study found no adverse effect on survival when axillary node dissection was avoided in patients with early breast cancer and limited sentinel node involvement.

For patients with breast cancer and metastases in the sentinel nodes, axillary dissection has been standard treatment. Recently, however, concerns have been voiced that, for patients with limited sentinel-node involvement,

axillary dissection might represent overtreatment, with side-effects including lymphoedema, pain and reduced arm movement.

In the current study, Viviana Galimberti and colleagues, from the European Institute of Oncology, Milan, Italy, set out to determine whether no axillary dissection was non-inferior to axillary dissection in patients with one or more micrometastatic (≤2 mm) sentinel nodes and tumours of maximum 5 cm. Altogether, 6681 patients from 17 centres were screened for enrolment, with only 934 (14%) meeting the requirement of micrometastatic sentinel nodes. Between April 2001 and February 2010, the 934 patients were randomised 1:1 to either axillary dissection (*n*=464) or no axillary dissection (*n*=467).

At a median follow-up of five years, disease-free survival was 84.4% in the group with axillary dissection versus 87.8% in the group without (*P*=0.16). Furthermore, the five-year cumulative incidence of breast cancer events was 10.8% in the group with axillary dissection versus 10.6% in the group without axillary dissection (*P*=0.90).

In the group that underwent axillary dissection, grade 3–4 long-term surgical events included one of sensory neuropathy, three of lymphoedema, and three of motor neuropathy. In the group without axillary dissection one grade 3 motor neuropathy was reported. Accrual was slower than anticipated, mainly because small metastases were rare.

These findings, write the authors, are consistent with the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial in 2011, which randomly assigned 856 patients with limited macrometastatic sentinel node involvement (not more than two metastatic sentinel nodes) to axillary dissection versus no further axillary treatment. After 6.3 years the ACOSOG Z0011 trial found the groups showed no differences for any endpoints.

"It is possible that our trial and ACOSOG Z0011 will change clinical practice, sparing many patients with early breast-cancer axillary dissection, especially when the sentinel node is minimally involved, thus reducing surgical complications related to axillary dissection with no adverse effect on survival," write the authors.

Already, they add, the 2011 St Gallen Consensus Conference has moved in the direction of recommending that micrometastases in a single sentinel node should not be an indication for axillary dissection irrespective of the type of breast surgery given. In an accompanying commentary, John Benson, from Cambridge University Teaching Hospitals Trust, UK, writes: "These results of IBCSG 2301 are practice changing when co-interpreted with those of Z0011."

■ V Galimberti, B Cole, S Zurrida et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* April 2013, 14: 297–305

■ J Benson. Management of breast-cancer patients with sentinel-node micrometastases. *ibid*, pp 266–267

Questionnaire explores patient reluctance for RCTs

■ British Journal of Cancer

Altruism, and the belief that trials offer the best available treatment option represent the top reasons patients decide to enter into randomised clinical trials (RCTs), a UK study has reported.

Worldwide recruitment into RCTs has remained fairly low, impeding the early introduction of efficacious treatment into clinical settings. Understanding some of the reasons why patients reject participation in trials is considered useful to inform future patient communication and trial design.

In the current study, Val Jenkins and colleagues from the University of Sussex, Brighton, UK, administered two questionnaires, each with 16 questions, to examine the reasons why patients accepted or declined trial entry.

The first questionnaire examined reasons why patients accepted or declined trial entry, with the initial question establishing whether or not they had agreed to trial entry. The second questionnaire explored patients' perceptions about their healthcare professionals' information giving, with the initial question addressing who had spoken with them about the trial (e.g. research nurse or clinician).

For each statement, patients registered their agreement on a scale of 0 to 4 (0=strongly agree, 1=agree to some extent, 2=unsure, 3=disagree to some extent, 4=strongly disagree). Both questionnaires were given to patients by research nurses, with patients completing the answers at home once they had decided whether or not they would take part.

Questionnaires were completed by 358 out of the 486 patients approached (74%). The responses showed that 291 (81%) had joined a RCT while 56 (16%) had declined and 11 (3%) were undecided. The primary reason given for trial acceptance was altruism (40%; 110/275), followed by the belief that the trial offered the best treatment (18%; 50/275). The main reasons given for declining the trial were trust in the doctor (28%;12/43) and wishing the doctor to choose (14%; 6/43).

A noteworthy finding was that 44% of responders declining trials (20/45) had been offered a trial comparing standard treatment with novel drugs or different durations of standard treatment.

Patients indicated that trials were discussed more often by research nurses (65%; 224/345) than clinicians (29%; 101/345) or both (6%; 20/345). Communication was good, with 97% of trial accepters and 100% of trial decliners saying their healthcare professional used clear and understandable language; 99% of accepters and 100% of decliners understood that trial entry was voluntary.

"These findings present a very positive picture of the communication received by

patients in the United Kingdom about clinical trial participation, treated by the MDTs being studied. Poor communication did not seem to be a determining factor as to whether or not patients joined a trial, but trial design, especially if one arm appeared to be offering less treatment, did seem to deter some," conclude the authors.

Trials comparing shorter durations, they add, could evoke anxiety about efficacy. "In contrast, trials that had a standard drug plus or minus a new drug appeared more attractive, perhaps because the patient would not feel they were losing out and may even gain an extra treatment," write the authors.

■ V Jenkins, V Farewell, D Farewell et al. Drivers and barriers to patient participation in RCTs. *Br J Cancer* 16 April 2013, 108:1402–07

Study quantifies risk of ischaemic heart disease from ionising radiation

■ New England Journal of Medicine

The increased risk of ischaemic heart disease caused by exposure to ionising radiation during radiotherapy for breast cancer is proportional to the mean dose to the heart, with women with pre-existing cardiac risk factors showing greater absolute increases in risk, a population-based case–control study has found. Risk, the study found, begins within a few years of exposure and continues for at least 20 years.

Radiation therapy has evolved as a critical component of treatment for women with breast cancer who have undergone breast-conservation surgery, and for those with a high risk of recurrence who have undergone mastectomy. While older radiation techniques have been associated with subsequent cardiac disease, less is known about associations with modern radiation techniques.

In the current study, Sarah Darby and colleagues, from the Clinical Trial Service Unit at the University of Oxford, UK, undertook an investigation relating the risk of ischaemic heart disease after radiotherapy to each woman's radiation dose to the heart, taking into account any cardiac risk factors that individuals had at the time of radiotherapy.

Altogether 2168 women who received external-beam radiotherapy for invasive breast cancer between 1958 and 2001 in Sweden and Denmark were followed up. Of these, 963 experienced major coronary events (defined as a diagnosis of myocardial infarction, coronary revascularisation or death from ischemic heart disease), and 1205 acted as controls who did not. Data on each woman's medical history prior to diagnosis with breast cancer, tumour characteristics and radiotherapy treatment were obtained from hospital oncology department records.

Results show that, among the case-defining major coronary events, 44% occurred less than 10 years after diagnosis of breast cancer, 33% occurred 10 to 19 years afterwards, and 23% occurred 20 or more years afterwards. Overall, the estimated mean dose of radiation to the heart was 6.6 Gy for women with tumours in the left breast, 2.0 Gy for women with tumours in the right breast, and 4.9 Gy overall. Furthermore, the rate of major coronary events increased by 7.4% for each increase of 1 Gy in the mean radiation dose delivered to the heart.

Although the overall rate ratio for a major coronary event was 6.67-fold higher for women with a history of ischemic heart disease as compared to women with no such history, the proportional increase in the rate of major coronary events per gray was similar.

"The relevance of our findings to a woman receiving radiotherapy for breast cancer today is that they make it possible to estimate her absolute risk of radiation-related ischemic heart disease. This absolute risk can be weighed against the probable absolute reduction in her risk of recurrence or death from breast cancer that would be achieved with radiotherapy," write the authors.

In an accompanying commentary, Javid Moselehi, from Harvard Medical School, Boston, Massachusetts, writes that the study underlines the need for greater collaboration between oncologists and cardiologists. "An important lesson for the oncologist may be that the time to address concerns about cardiovascular 'survivorship' is at the time of cancer diagnosis... Similarly, cardiologists need to assess prior exposure to radiation therapy as a significant cardiovascular risk factor in survivors of breast cancer."

■ S Darby, M Ewertz, P McGale et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *NEJM* 14 March 2013, 368:987–998

■ J Moselehi. The cardiovascular perils of cancer survivorship. *ibid* pp 1055–56

Noninvasive ventilation reduces dyspnoea in patients near end of life

■ Lancet Oncology

Noninvasive ventilation (NIV) is more effective than oxygen therapy for reducing dyspnoea in cancer patients nearing the end of their life, and also allows lower doses of morphine, reports a feasibility study. The study, write the authors, is to the best of their knowledge the first to assess the feasibility of NIV as a palliative measure in comparison with oxygen in terminally ill patients.

Respiratory symptoms and dyspnoea are commonly reported in patients with solid tumours, with prevalence estimated to range from 20% to 80%. There have been suggestions that NIV, a system supporting breathing without an endotracheal tube, might offer an alternative option to relieve dyspnoea. NIV works by delivering positive pressure to support inhalation and prevents complete exhalation, thereby facilitating breathing.

In the current study, Stefano Nava and

colleagues, from Azienda Ospedaliera Universitaria, Bologna, Italy, enrolled consecutive patients with solid tumours from seven centres in Italy, Spain and Taiwan. The patients, who had been admitted to hospital because of acute respiratory failure and distress, had life expectancies of less than six months and had chosen to receive palliative care only.

Between January 2008 and March 2011, 441 consecutive patients were screened for eligibility; 234 were eligible for recruitment and 200 (85%) were randomly allocated to treatment. Prior to randomisation, each patient was given a 5- to 10-minute demonstration to familiarise themselves with NIV and allow their willingness to participate to be assessed.

Results show dyspnoea decreased more rapidly in the NIV group than in the oxygen group; the Borg score decreased by an average of 0.58 in the NIV group compared to 0.23 in the oxygen group (P=0.0012). The total dose of morphine during the first 48 hours was 26.9 mg in the NIV group compared to 59.4 mg for the oxygen group (P<0.05).

Eleven of 99 patients in the NIV group stopped treatment early, compared to no patients in the oxygen group. Reasons for discontinuation included claustrophobia, suffocation, anxiety, sense of imminent death, not understanding the protocol, and requests from relatives.

In-hospital mortality was similar in the two groups. However, in patients with hypercapnia, in-hospital survival and survival six months after discharge were better in those who received NIV than those who received oxygen therapy (HR for all deaths, 0.41; 95%CI 0.21–0.80).

"One of the main concerns about the use of NIV is the supposed low acceptance rate, especially when patients are severely dyspnoeic and anxious. ...When the technique was carefully explained and patients were given a brief trial period on NIV, and when they were assured that withdrawal from NIV was possible at any time, NIV was, in general, well accepted," write the authors.

In an accompanying commentary, Anita Simonds from the Royal Brompton and Harefield NHS Foundation, London, UK, writes, "Clinical teams should set goals such as reduction in dyspnoea or symptom burdens when the aim of NIV is to palliate symptoms rather than act as life support, so that if these objectives are not achieved NIV can be rapidly withdrawn and will not add to a patient's burdens."

■ Stefano Nava, M Ferrer, A Esquinas et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. *Lancet Oncol* March 2013, 14: 219–227

■ A Simonds. Palliating breathlessness in patients with advanced cancer. *ibid* pp 181–182

Spin plays a role in reporting of clinical trials

■ Annals of Oncology

Investigators commonly use spin to emphasize secondary results when primary endpoints are not significant, a Canadian study has reported. The analysis also revealed deficiencies in the reporting of severe toxicities.

Reviews have suggested that a substantial proportion of clinical trials have suboptimal reporting of harm, especially of severe toxicity. In the current study, Ian Tannock and colleagues, from Princess Margaret Hospital, Toronto, Canada, evaluated the quality of reporting of primary endpoints and of toxicity in randomised controlled trials for breast cancer. The investigators chose to focus on breast cancer, given that it is the most common malignancy in women, has substantial mortality and is a cancer site involving a large number of trials.

Using PUBMED, the investigators identified 164 clinical trials for breast cancer (148 for systemic therapy, 11 for radiation therapy and five for surgical therapy) published between 1995 and 2011. For inclusion, trials needed to be phase III studies, published in English, including patients aged over 18, and have sample sizes greater than 200 patients. There was a focus on trials that had the potential to change clinical practice.

Results showed that 72 studies (43.9%) were positive, with a significant P-value for the difference in primary endpoint favouring the experimental arm, compared with 92 (56.1%) with a non-significant P-value. Of the 92 trials with a negative primary endpoint, 59% used secondary endpoints to suggest benefits for experimental therapy. Furthermore, only 32% of articles indicated the frequency of grade 3 and 4 toxicities in the study. When the investigators rated the reporting of toxicity on a hierarchical scale, ranging from 1 (excellent) to 7 (very poor), they rated 34 trials as 7, 55 as 6, and 21 as 5.

Although 67% of the trials were industry sponsored, the authors found no association between industry sponsorship and biased reporting of either efficacy or toxicity. The majority, 150 trials (91.4%), were published in medium- or high-impact journals, with the median impact factor for all the journals calculated as 19.

To avoid selection for publication of positive trials, and/or publication of a subset of the original recorded outcomes on the basis of the results, write the authors, registration of trials is now mandatory. However, ClinicalTrials.gov was only established in 2002, with just 18% of the 164 trials analysed in the study registered. "Trial registration does not necessarily remove bias in reporting outcome, although it makes it easier to detect," they add.

Bias in the reporting of efficacy and toxicity, conclude the authors, remains prevalent. "Clinicians, reviewers, journal editors and regulators should apply a critical eye to trial reports and be wary of the possibility of biased reporting. Guidelines are necessary to improve the reporting of both efficacy and toxicity," they write.

■ F Vera-Badillo, R Shapiro, A Ocana et al. Bias in reporting of end points of efficacy and toxicity in randomized, clinical trials for women with breast cancer. *Ann Oncol* May 2013, 24: 1238–44