newsround

Selected reports edited by Janet Fricker

Glioblastoma: temozolomide offers alternative to radiotherapy in elderly patients

■ The Lancet

Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options for elderly patients with glioblastoma, a phase III study from the Nordic Clinical Brain Tumour Study Group (NCBTSG) has found.

In 2004 chemoradiotherapy with temozolomide became the standard of care for patients with glioblastoma, but its introduction was based on a pivotal study in which patients were aged 70 years or younger. In other studies, increasing age has been shown to be a negative prognostic factor, leading to the suggestion that elderly and frail patients might not be viewed as candidates for combined therapy.

To define an evidence-based treatment for patients aged 60 years or older with glioblastoma, NCBTSG investigators undertook a randomised trial to compare health-related quality of life and safety in patients randomised to single-agent temozolomide chemotherapy, short-course hypofractionated radiotherapy (34.0 Gy administered in 3.4 Gy fractions over two weeks) or standard six-week radiotherapy (60.0 Gy administered in 20.0 Gy fractions over six weeks). Both patients and staff were aware of treatment assignments.

Between February 2000 and June 2009, 342 patients with newly diagnosed, histologically confirmed glioblastoma (WHO grade IV astrocytoma) from 28 centres in Austria, Denmark, France, Norway, Sweden, Switzerland and Turkey were recruited.

In the study, 291 patients were randomised across three treatment groups: temozolomide (n=93), hypofractionated radiotherapy (n=98), and standard radiotherapy (n=100). An additional 51 patients were randomised across only two groups: temozolomide (n=26) and hypofractionated radiotherapy (n=25).

Results for the three-group randomisation show that median overall survival was 6.0 months for standard radiotherapy versus 8.3 months with temozolomide (HR 0.70, 95%CI 0.52–0.93, P=0.01); and 7.5 months with hypofractionated radiotherapy (HR 0.85, 95%CI 0.64–1.12, P=0.24).

In the two-group randomisation, overall survival was 8.4 months for patients who received temozolomide versus 7.4 months for patients who received hypofractionated radiotherapy (HR 0.82, 95%CI 0.63–1.06; P=0.12).

For patients older than 70 years, survival was better with temozolomide (HR 0.35; P<0.001) and with hypofractionated radiotherapy (HR 0.59; P=0.02), in comparison with standard radiotherapy.

An additional finding was that patients treated with temozolomide who had tumour MGMT promoter methylation showed significantly longer survival than those without (HR 0.56; P=0.02).

As expected, the most common grade 3–4 adverse events in the temozolomide group were neutropenia (n=12) and thrombocytopenia (n=18).

"We found that temozolomide chemotherapy is a potential alternative to radiotherapy in elderly and frail patients," write the authors. The results, they add, support the predictive value of MGMT promoter methylation as a useful biomarker in guiding treatment decisions around temozolomide.

In an accompanying commentary, Phioanh Leia Nghiemphu and Timothy Cloughesy, from the University of California at Los Angeles, write, "The Nordic study is a well balanced randomised trial that provides provocative results and greatly contributes to the understanding of geriatric neuro-oncology. For patients aged 70 years and younger, radiation at least did not negatively affect survival and provides insight into a molecular subgroup that might be well suited to treatment with temozolomide."

A collective effort towards systematic prioritisation of the effects of all factors on prognosis, they add, will enable classification of prognostic subgroups for prospective investigation and eventually lead to definition of relevant optimum treatments.

■ A Malmström, B Henning Gronberg, C Marosi et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncology*, September 2012, 13:916–926

■ P Nghiemphu, T Cloughesy. Glioblastoma therapy in the elderly: one age does not fit all. *ibid*, pp 857–858

R-CHOP best for older patients with mantle-cell lymphoma

■ New England Journal of Medicine

For older patients with mantle-cell lymphoma, a rituximab-based chemotherapy regimen followed by rituximab maintenance therapy improves survival, according to the results of a study by the European Mantle Cell Lymphoma Network.

Treatment options for older patients with mantle-cell lymphoma are limited, as the standard first-line therapy approach of high-dose cytarabine, followed by autologous stem-cell transplantation, is usually not feasible. The median age at diagnosis for mantle-cell lymphoma is about 65 years.

In the current study, Habbeje Kluin-Nelemans and colleagues, from the Groningen University Medical Centre, in the Netherlands, compared two induction regimens, followed by two different maintenance therapies for those showing a response.

Between January 2004 and October 2010 investigators randomly assigned 560 patients aged 60 years or older with mantle-cell lymphoma, stage II to IV, who were not eligible for high doses to one of two alternative treatment arms: six cycles of rituximab, fludarabine and cyclophosphamide (R-FC) every 28 days or eight cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 21 days. Altogether 532 of these patients were included in the intention-to-treat analysis and 485 in the primary analysis.

Results showed that the four-year survival rate was 47% for R-FC versus 62% for R-CHOP (*P*=0.005). Furthermore, 10% of patients in the R-FC group died during the first remission versus 4% in the R-CHOP group.

Complete remission rates were 40% for R-FC versus 34% for R-CHOP (*P*=0.10), and progressive disease was 14% for R-FC versus 5% for R-CHOP.

Among those re-randomised to maintenance therapy, 58% of those receiving rituximab were in remission after four years versus 29% receiving interferon-alpha (HR for progression or death 0.55, 95%CI 0.36–0.87, *P*=0.01). Furthermore, among patients who had a response to R-CHOP, the four-year survival of patients receiving maintenance therapy with rituximab was 87%, versus 63% for interferon-alpha (*P*=0.005).

"In conclusion, older patients with mantle-cell lymphoma who have a response to R-CHOP and continue to receive rituximab as maintenance therapy have a longer life expectancy than those who receive maintenance therapy with interferon-alfa," write the authors.

The outcomes for R-FC, they add, were disappointing, given the high expectations that this regimen had in the early 2000s. In future, they add, it might be "attractive" to combine rituximab-based maintenance regimens with other drugs shown to be active against mantle-cell lymphoma, such as bendamustine or molecularly targeted approaches.

"However, physicians need to be aware of the potential interactions between the initial therapy and the maintenance regimen," write the authors.

■ H Kluin-Nelemans, E Hoster, O Hermine et al. Treatment of older patients with mantle cell lymphoma. *NEJM* 9 August 2012, 367:520–531

Observation effective in prostate cancer with low PSA

■ New England Journal of Medicine

For men with localised prostate cancer detected through prostate-specific antigen (PSA) testing, radical prostatectomy delivers no survival benefits over 12 years follow-up in comparison to observation alone, the PIVOT study has reported. Subgroup analyses of the US study, however, suggest surgery reduces mortality among prostate cancer patients with high PSA levels.

Although the lifetime risk of receiving a diagnosis of prostate cancer is about 17%, the risk of dying from the disease is approximately 3%, suggesting conservative management may be appropriate for some men. But the observation option is rarely offered due to lack of evidence from randomised trials.

In the Prostate Cancer Intervention versus Observation Trial (PIVOT) study, Tim Wilt, from the University of Minnesota School of Medicine, Minneapolis, and colleagues conducted a randomised trial to compare radical prostatectomy with observation in men who had received a diagnosis of clinically localised prostate cancer in the early era of PSA testing. Between November 1994 and January 2004, 731 men with localised prostate cancer were randomised to radical prostatectomy (*n*=364) or observation (*n*=367). Patients, who had a mean age of 67 years, were recruited from 44 Department of Veterans Affairs sites and eight National Cancer Institute sites and followed through until January 2010.

Results during a median follow-up of 10 years show 47.0% of men assigned to radical prostatectomy died compared with 49.9% assigned to observation (HR 0.88, 95%CI 0.71–1.08; *P*=0.22). Additionally, 5.8% of men assigned to radical prostatectomy died from prostate cancer or treatment compared with 8.4% assigned to observation (HR 0.63, 95%CI 0.36–1.09; *P*=0.09). During the first 30 days after surgery, perioperative complications occurred in 21.4% of men undergoing radical prostatectomy, with the most common complication being wound infections (4.3%).

Among men with a PSA value greater than 10 ng/ml, surgery reduced all-cause mortality by 13.2%. Among men with intermediate-risk tumours (determined by a PSA value of 10.1–20.0 ng/ml, a Gleason score of 7, or a stage T2b tumour), those randomly assigned to surgery had a 31% relative reduction in all-cause mortality compared with those assigned to observation.

"Our findings support observation for men with localized prostate cancer, especially those who have a low PSA value and those who have low-risk disease," write the authors. The study, they add, was conducted in the early era of PSA testing. "The current practices of performing repeated PSA testing, using a lower PSA

threshold for biopsy, obtaining more tissue-biopsy cores, and performing a repeat biopsy after initially negative findings increase the detection of smaller volume indolent cancers. ...These factors increase the likelihood of over diagnosis and overtreatment."

In an accompanying commentary, Ian Thompson from the University of Texas Health Science Center, San Antonio, and Catherine Tangen from the Fred Hutchinson Cancer Center, Seattle, stress that the men most likely to benefit from therapy are those whose prostate cancers pose the greatest risk of death from cancer. "The screening, detection, and treatment we provide must focus on cancers that matter, and future clinical trials must do so as well," they write.

■ T Wilt, M Brawer, K Jones. Radical prostatectomy versus observation for localised prostate cancer. *NEJM* 19 July 2012, 367:203–213

■ I Thompson, C Tangen. Prostate cancer – uncertainty and a way forward. *ibid* pp 270–271

Pyridoxine not recommended in hand-foot syndrome

■ **British Journal of Cancer**

While pyridoxine (vitamin B6) may reduce the incidence of severe hand-foot syndrome (HFS) and the need for capecitabine dose modifications in patients with advanced colorectal or breast cancers, no antitumour benefits were detected, the CAP-IT study has reported. Routine use of pyridoxine for HFS, conclude the UK investigators, should not be recommended.

Pyridoxine is frequently used to treat capecitabine-induced HFS. Since HFS resembles the rat disease acrodynia, known to be caused by pyridoxine deficiency, treatment with pyridoxine has been proposed. There is, however, no evidence for benefit. In the current study, Pippa Corrie and colleagues from Addenbrooke's Hospital, Cambridge, performed a randomised placebo-controlled trial to determine whether pyridoxine avoided the need for capecitabine dose modifications and furthermore improved outcomes.

Altogether 106 patients with a median age of 73 years scheduled for palliative single-agent capecitabine (65% of whom had colorectal cancer and 35% breast cancer) were randomised in a 1:1 ratio, between December 2004 and June 2009, to receive either concomitant pyridoxine (50 mg; *n*=53) or matching placebo (*n*=53) three times daily, commencing on the day capecitabine chemotherapy was initiated. Treatment continued until disease progression, toxicity or patient preference. After discontinuation, patients were followed up for 12 weeks.

Results showed that 37% of patients randomised to pyridoxine avoided capecitabine dose modifications versus 23% randomised to placebo (RR 0.59, 95%CI 0.29–1.20; *P*=0.15). Furthermore, 9% of patients in the pyridoxine group experienced grade 3/4 HFS-related adverse events versus 17% in the placebo group (*P*=0.26). There was a trend towards pyridoxine decreasing progression-free survival (PFS), with a median PFS duration of 7.4 months for pyridoxine and 9.9 months for placebo (HR 1.62, 95%CI 0.91–2.88; *P*=0.095).

"Pyridoxine appeared to reduce the incidence of grade 3/4 HFS and the need for capecitabine dose modifications, although this did not translate into an improvement in outcome from chemotherapy itself; the trend towards poorer PFS in the pyridoxine arm was not statistically significant," write the authors. "Whether pyridoxine might in fact negatively influence chemotherapy efficacy is intriguing, although not conclusive," they add.

The authors also refer to an earlier study, which reported significantly lower tumour responses to capecitabine at the higher pyridoxine dose level, while a second study, involving use of pyridoxine in advanced ovarian cancer, found it reduced durations of response to treatment with hexamethylamine plus cisplatin.

■ P Corrie, R Bulusu, C Wilson, et al. A randomised study evaluating the use of pyridoxine to avoid capecitabine dose modifications. *Br J Cancer* 7 August 2012, 107:585–587

Study suggests new standard of care for platelet transfusions

■ **The Lancet**

Therapeutic platelet transfusions could become the new standard of care for patients with haematological malignancies who have received autologous stem cell transplantation, a German study suggests. Prophylactic platelet transfusion, however, should remain the standard for patients with acute myeloid leukaemia for whom special attention is needed due to increased risk of central nervous system (CNS) bleeding.

Routine prophylactic platelet transfusion is the standard of care for patients with severe thrombocytopenia with morning platelet counts of $10x10^9$ per litre or lower. However, whether such transfusions are necessary for clinically stable patients with no bleeding has long been debated. Small studies performed 30 years ago showed favourable results for the therapeutic strategy (where transfusions are offered following bleeds), but these results are no longer considered applicable to current clinical practice due to changes in chemotherapy dose intensities and supportive care.

In 2005 and 2006 two single-centre pilot studies showed that a new strategy of therapeutic platelet transfusion was feasible, with no increased risk in major bleeding and a substantially reduced number of platelet transfusions compared with historical controls. In the current study, the same team, led by Hannes Wandt from the Klinikum Nuremberg Nord, Germany, investigated whether these results could be reproduced prospectively in a multicentre randomised study.

In the study, patients aged 16–80 years undergoing intensive chemotherapy for acute myeloid leukaemia or autologous haematopoietic stem-cell transplantation for haematological cancers were randomised to receive platelet transfusions either when bleeding occurred (therapeutic strategy, *n*=199) or when morning platelet counts were $10x10^9$ per litre or lower

(prophylactic strategy, *n*=197). Altogether 190 of the patients had acute myeloid leukaemia and 201 had undergone autologous transplantation.

The study was undertaken between February 2005 and May 2010 at eight haematology centres in Germany.

Results show that, for all patients, the primary endpoint of platelet transfusions occurred in 2.44% of patients in the prophylactic group versus 1.63% in the therapeutic group (*P*<0.0001). For those with acute myeloid leukaemia, transfusions occurred in 2.68% randomised to the prophylactic group versus 1.83% to the therapeutic group, representing a 31.6% reduction (*P*<0.0001). While for those who had autologous transplantation, transfusions occurred in 1.8% in the prophylactic group versus 1.18% in the therapeutic group, representing a 34.2% reduction (*P*=0.0193).

For patients undergoing autologous transplantation, randomisation to the therapeutic arm did not increase the risk of major haemorrhage; but for those with acute myeloid leukaemia in the therapeutic arm, the risk of non-fatal grade 4 bleeding significantly increased (mostly CNS) compared to the prophylactic group (*P*=0.0095).

"Our findings show that the number of platelet transfusions was significantly lower, by roughly a third, in the therapeutic group than in the prophylactic group. However, this clinically meaningful difference must be weighed against the increased bleeding risk," write the authors.

The new strategy of therapeutic platelet transfusions in patients who have received autologous stem cell transplantation, they add, should be used only by haematology centres where staff are experienced in the approach and can react in a timely way to first signs of CNS bleeding.

In an accompanying commentary, Neil Blumberg and colleagues from the University of Rochester Medical Center, New York, write, "The emerging hypothesis, ... is that transfused platelets might be promoters of arterial and venous thrombosis, tumour growth, and metastasis. These possibilities provide additional reasons to favour a restrictive policy for platelet transfusion in view of the moderate benefits of transfusion shown in autologous transplant patients."

■ H Wandt, K Schaefer-Eckart, K Wendelin et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet*, published online 7 August 2012, doi:10.1016/S0140-6736(12)60689-8

■ N Blumberg, J Heal, G Phillips, et al. Platelets – to transfuse or not to transfuse. *ibid*, doi:10.1016/S0140-6736(12)60983-0

Survival advantage for centralisation of vulvar surgery

■ European Journal of Cancer

Centralisation of care for women with vulvar squamous cell carcinoma (SCC) is associated with improved survival, a Dutch study has reported.

In 2000, guidelines from the Dutch Society of Obstetrics and Gynaecology recommended centralisation of care for patients with vulvar SCC. Benefits identified for this approach included the development of expertise, and the opportunity to give patients appropriate treatment from experienced clinicians using new techniques that might improve prognosis and/or lower treatment-related morbidity. The strategy was also thought to facilitate training and research.

The cornerstone of treatment for vulvar carcinoma is surgery, which offers an excellent chance of cure. In other rare malignancies, such as oesophageal and pancreatic carcinomas, associations have been found between the volume and/or specialisation of a hospital on the one hand and better survival on the other hand. In recent years, treatment of patients with early-stage vulvar SCC has shifted from inguinofemoral lymphadenectomy to the sentinel lymph node dissection (SLND) procedure. To meet quality standards, it has been suggested that surgeons should perform SLND surgery at least 510 times per year. For a rare tumour such as vulvar SCC, with an annual incidence of one to two cases per 100,000 women, this would require centralisation.

In the current study, Loes van den Einden and colleagues, from Radboud University, Nijmegen Medical Centre, in the Netherlands, set out to determine whether guidelines had been adopted and whether such adoption had resulted in improvements in survival. The guidelines were introduced in 2000. For the study, data on all patients diagnosed with vulvar malignancies between 1989 and 2008 in the eastern part of the Netherlands were retrieved from the population-based cancer registry held by the Comprehensive Cancer Centre IKNL. Data for patients diagnosed before the introduction of guidelines (1989–1999) were compared with those for patients diagnosed after (2000–2008).

A total of 382 patients with vulvar SCC with invasion >1 mm, who had an indication for groin surgery, were included in the analysis. In the first decade, 62% (123 out of 198 patients) were treated in a specialised oncology centre, which increased to 93% (172 out of 184 patients) in the more recent period (*P*<0.0001). The five-year relative survival was 69% for the first period, compared to 75% for the second period. After adjustment for age and stage, being treated in a specialised oncology centre was found to be an independent prognostic factor for survival. Patients treated in a specialised oncology centre in the period 2000–2008 appeared to have comparable five-year relative survival rates compared to patients treated in specialised centres in the period 1989–1999.

"In conclusion, the present study showed that centralisation of the treatment of patients with vulvar SCC who need groin surgery has been well adopted in the Eastern part of the Netherlands. Being treated in a specialised oncology centre is associated with a better survival," write the authors.

■ L van den Einden, K Aben, L Massuger et al. Successful centralisation of patients with vulvar carcinoma: a population-based study in the Netherlands. *Eur J Cancer*, September 2012, 48:1997–2003