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Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial

Cuzick J , Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, Saunders C, Roche N, Mansel RE, von Minckwitz G, Bonanni B, Palva T, Howell A: on behalf of the IBIS-II investigators. The Lancet; Dec 12, 2013.

Background: Aromatase inhibitors effectively prevent breast cancer recurrence and development of new contra-lateral tumours in postmenopausal women. We assessed the efficacy and safety of the aromatase inhibitor anastrozole for prevention of breast cancer in postmenopausal women who are at high risk of the disease. **Methods:** Between Feb 2, 2003, and Jan 31, 2012, we recruited postmenopausal women (40-70 years) from 18 countries into a double-blind randomised placebo-controlled trial. To be eligible, women had to have at increased risk of breast cancer (based on specific criteria). Eligible women were randomly assigned (1:1) by central computer allocation to receive 1mg oral anastrozole or matching placebo daily for 5 years. Randomisation was stratified by country and done with blocks of 6, 8 or 10. All trial personnel, participants, and clinicians were blinded to treatment allocation, and only the trial statistician was unmasked. The primary endpoint was histologically confirmed breast cancer (invasive cancers or non-invasive ductal carcinoma in situ). Analyses were done on by intention to treat. **Findings:** 1920 women were randomly assigned to receive anastrozole and 1944 to placebo. After a median follow-up of 5 years (IQR 3·0-7·1), 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) had developed breast cancer (hazard ratio 0·47, 95% CI 0·3-0·68, p<0·0001). The predicted cumulative incidence of all breast cancers after 7 years was 5·6% in the placebo group and 2·8% in the anastrozole group. 18 deaths were reported in the anastrozole group and 17 in the placebo group, and no specific causes were more common in one group than the other (p=0·836). **Interpretation:** Anastrozole can effectively reduce incidence of breast cancer in high-risk postmenopausal women. This finding, along with the fact that most of the side-effects associated with oestrogen deprivation could not be attributed to treatment, provides support for the use of anastrozole in postmenopausal women at high risk of breast cancer.

Reviewer's opinion: Breast cancer in women particularly with presence of high risk factors is common. The result of this trial, which was simultaneously presented at San Antonio Breast Cancer Symposium 2013 by Jack Cuzick from London, is encouraging and predictable considering similar data already available on chemo-prevention of breast cancer in these women. However, the challenge remains how to define 'women at increased risk' and target most appropriate individuals for true prevention. Moreover, it is doubtful that there will be any meaningful mortality gains with chemo-prevention using current agents like anatrazole (IBIS-II), exemestane (MAP.3 trial), tamoxifen or raloxifene. Though the incidence of side effects was small in IBIS-II, they cannot be ignored because 20% of the women had to discontinue the active treatment due to adverse events, and the nature of late side effects need to be explored. Compliance and optimum method of screening to detect the sub-clinical lesions as well as duration of therapy remain an issue. Aromatase inhibitors can be offered to only post-menopausal women and have no impact on the development of more aggressive hormone receptor negative tumours. – SU

Neuro-Oncology

Comparative study of IDH1 mutations in gliomas by immunohistochemistry and DNA sequencing

Agarwal S, Sharma MC, Jha P, Pathak P, Suri V, Sarkar C, Chosdol K, Suri A, Kale SS, Mahapatra AK, Jha P. Neuro-Oncology 2013; 15(6):718-26.

The IDH1 gene on chromosome 2q33.3 encodes the enzyme isocitrate dehydrogenase 1 (IDH1) that catalyses NADPH production via oxidative decarboxylation of isocitrate to alpha-ketoglutarate in the Krebs citric acid cycle. IDH1 mutation is an early step in gliomagenesis and has been identified in grades II and III astrocytomas, oligodendrogliomas (OG), oligoastrocytomas (OA), and secondary GBM, with implications on diagnosis and prognosis. About 90% of reported IDH1 mutations involve exon 4 at codon 132, histidine replacing arginine (R132H). Rarer ones include R132C, R132S, R132G, R132L, R132V, and R132P. Although these mutations are rare in the pediatric age group (patients aged ≥ 18 years), they seem to be associated with younger age at presentation and a better prognosis (progression-free survival) associated with grade II-IV gliomas. Most tests of IDH mutations are based on DNA sequencing is not available at every diagnostic centre. In addition, false-negative results arise due to limited sensitivity caused by inadequate tumour DNA. The results of immunohistochemistry (IHC), using mAb H09 for IDH1-R132 mutations as an alternative method, have been compared with those of DNA sequencing in 50 diffuse gliomas. Agreement between IHC and DNA sequencing was seen in 88% (44/50) cases. The other 6 cases were immunopositive with the DIA-H09 antibody. In 3 of these 6 cases, DNA sequencing showed no mutations, and an R132L mutation was found in the other 3 cases. Notably, 47% (14/30) of the immunopositive cases had only a fraction of tumour cells stained. This indicates that IHC is a quick and easy method of detecting IDH1-R132H mutations, but there may be some discrepancies between IHC and DNA sequencing.

Reviewer's opinion: IDH1 mutation testing is being used as a diagnostic tool in many neuropathology centres in the prognosis for brain tumour patients. A reliable and efficient method is needed for testing and ensuring the accuracy of the result. IHC testing for IDH1 mutation with an antibody for IDH1-R132H is used in clinical centres worldwide. The IHC method also compared with immunostaining results using H09 with direct DNA sequencing in 50 cases of diffuse glioma. IHC was more sensitive than DNA sequencing in detecting IDH1-R132H mutations, but awareness of the possibility of heterogenous staining pattern and cross-reactivity with variant mutant proteins was essential for correct interpretation of the results. A new finding was the cross-reactivity of IDH1-R132H monoclonal antibody with R132L protein in formalin-fixed paraffin-embedded sections. In view of the rarity of mutations other than R132H in gliomas, IHC testing of IDH1 mutation with a larger number of glioma cases is needed to assess the sensitivity and specificity of this immunostaining method. – QA

Neuro-Oncology

Enhancing drug delivery for boron neutron capture therapy of brain tumours with focused ultrasound

Alkins RD, Brodersen PM, Sodhi RN, Hynynen K. Neuro-Oncology 2013; 15(9):1225-35.

The dismal prognosis associated with glioblastoma is attributable not only to its aggressive and infiltrative behaviour, but to its location typically deep in the parenchyma of the brain. Surgical corridors and extent of resection are limited by the potential of further neurological injury. Photon-based radiation therapy is a mainstay of treatment, but causes significant collateral injury to the brain that worsens with time. In addition, the blood-brain barrier (BBB) limits the accumulation of many therapeutic agents, particularly in infiltrating cells advancing beyond the tumour margin. The blood-tumour barrier (BTB) is variably more permeable, but remains a significant obstacle to therapy. With regard in particular to the brain, therapies need to spare healthy tissue as much as possible, but many of those that have selective activity against malignant cells are hindered by the cerebrovasculature. Boron neutron capture therapy (BNCT) is a treatment whereby a 10B-containing drug preferentially accumulates in malignant cells and causes highly localised damage when exposed to epithermal neutron irradiation. 10B-enriched L-4-boronophenylalanine-fructose (BPA-f) complex uptake can be improved by enhancing the permeability of the cerebrovasculature with osmotic agents. This study used MRI-guided focused ultrasound in combination with injectable microbubbles to non-invasively and focally augment BPA-f uptake. In a 9L gliosarcoma model in Fisher 344 rats, the BBBs and BTBs were disrupted with pulsed ultrasound using a 558 kHz transducer and Definity microbubbles; BPA-f (250 mg/kg) was given intravenously for 2 h. 10B concentrations were estimated with imaging mass spectrometry and inductively coupled plasma atomic emission spectroscopy. The tumour to brain ratio of 10B was 6.7 $\pm$ 0.5 with focused ultrasound compared with 4.1 $\pm$ 0.4 in the control group ($P < 0.01$), corresponding to a mean tumour [10B] of 123 $\pm$ 25 ppm and 85 $\pm$ 29 ppm, respectively. 10B uptake in infiltrating clusters treated with ultrasound was 0.86 $\pm$ 0.10 times the main tumour concentration, compared with only 0.29 $\pm$ 0.08 in controls. This suggests that ultrasound increases the accumulation of 10B in the main tumour and infiltrating cells. These findings, in combination with the expanding clinical use of focused ultrasound, may offer improvements in BNCT and the treatment of glioblastoma.

Reviewer's opinion: Due to the unique features of brain tumours, e.g. location, cellular heterogeneity, infiltrative invasion and existence of BBB, prognosis of patients remains poor despite current advances in therapeutics. One of the greatest challenges currently being faced in the successful treatment of brain tumour patients is the development of tumour-specific therapy that minimises damage to healthy surrounding brain tissue. The authors investigated enhanced drug delivery in boron neutron capture therapy with focused ultrasound. The findings are interesting and have clinical implication of this emerging therapeutic strategy. However, evidence of improved survival is lacking and the findings need confirmation by using a larger numbers of animals. Its clinical application in human patients requires optimisation to have any benefit over existing conventional therapy. – QA

New England Journal of Medicine

A Randomised Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Gilbert MR, Dignam JJ, et al. New England Journal of Medicine; 2014;370; 699-708.

Background: Concurrent treatment with temozolomide and radiotherapy followed by maintenance temozolomide is the standard of care for patients with newly diagnosed glioblastoma. Bevacizumab, a humanised monoclonal antibody against vascular endothelial growth factor A, is currently approved for recurrent glioblastoma. Whether the addition of bevacizumab would improve survival among patients with newly diagnosed glioblastoma is not known. **Methods:** In this randomised, double-blind, placebo-controlled trial, we treated adults who had centrally confirmed glioblastoma with radiotherapy (60 Gy) and daily temozolomide. Treatment with bevacizumab or placebo began during week 4 of radiotherapy and continued for up to 12 cycles of maintenance chemotherapy. At disease progression, the assigned treatment was disclosed, and bevacizumab therapy could be initiated or continued. The trial was designed to detect a 25% reduction in the risk of death and a 30% reduction in the risk of progression or death, the 2 co-primary end-points with the addition of bevacizumab. **Results:** A total of 978 patients were registered and 637 underwent randomisation. There was no significant difference in the duration of overall survival between the bevacizumab group and the placebo group (median, 15.7 and 16.1 months, respectively; hazard ratio, 1.13). Progression-free survival (PFS) was longer in the bevacizumab group (10.7 vs. 7.3 months; hazard ratio 0.79). There were modest increases in rates of hypertension, thromboembolic events, intestinal perforation, and neutropenia in the bevacizumab group. Over time, an increased symptom burden, a worse quality of life and a decline in neuro-cognitive function were more frequent in the bevacizumab group. **Conclusions:** First-line use of bevacizumab did not improve overall survival in patients with newly diagnosed glioblastoma. PFS was prolonged but did not reach the pre-specified improvement target. – SU