THURSDAY 25 OCTOBER 2001

Controversies

1351

What should be the standard

Abstract not received.

1352

Controversies in the HER2 positive patients: how to best identify

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Different tests are now available to establish the HER2 status of a primary breast carcinoma. The easiest and cheapest method by far is immunohistochemistry (IHC) with an appropriate reagent and a well set-up methodology including positive and negative controls. An alternative methodology, 5–10 times more expensive than immunohistochemistry, is 'fluorescent in situ hybridization' (FISH) which allows for the identification of HER2 gene amplification instead of the overexpressed protein. The great majority of cases scoring strongly positive (3+) with homogeneous membrane labelling by IHC, representing about 15–16% of all breast carcinomas, were also found to display an amplification of the HER2 gene by FISH analysis. The cases scoring 2+-positivity by IHC, on the contrary, displayed gene amplification in only one third of the cases. The great majority of cases negative or focally positive by IHC were also FISH-negative. The category scoring 2+ by IHC, representing 9–10% of all breast carcinomas, is the only actual category which opens controversies for the evaluation of HER2 status.

The choice of methodology should be based upon the clinical application for which HER2 status is required and more importantly, the materials available for this determination. If HER2 status is required prior to surgery, for example for the selection of neo-adjuvant therapy with drugs and/or Herceptin and only needle biopsies are available, FISH tests represents the most appropriate methodology for the evaluation of HER2 status since nuclei are definitively better conserved in this biopsy material than cell membranes. On the other hand, cases in which the tumour specimen is available, IHC is still the recommended methodology and only 10% of the cases scoring 2+ might require a confirmatory FISH test. Clinical trials with Herceptin indicated that only FISH-positive cases, both those with IHC 3+ and those with IHC 2+, seemed to respond to therapy with the monoclonal antibody, whereas IHC-2+, FISH-negative cases were poorly responsive. Since the target for Herceptin is the membrane overexpressed protein and not the amplified gene, theoretically IHC was expected to be a better predictor of response. One possible explanation comes from our data on HER2 expression in tumour specimens sampled in the same patient, which indicated a fluctuation of IHC HER2 score in 2+-positive tumours according to the hormonal situation of the patient whereas 3+ cases were stable in their expression. This finding suggests that some Herceptin-treated cases included in the trial due to their 2+ score

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Combination is the way to go

Abstract not received.

1354

Monotherapy is the way to go

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Many years ago there was controversy on whether endocrine therapy should be given before chemotherapy (CT) or concurrently for metastatic breast cancer (MBC). Two separate trials showed that survival was at least as good using endocrine monotherapy first, followed by chemotherapy at relapse [Cavalli Br Med J 286: 5, 1983; ANZ Breast Cancer Trials Group J Clin Oncol 4: 186, 1986]. A similar issue has now arisen concerning the use of Herceptin (H) before or concurrently with chemotherapy for MBC.

Current practice with H is based on a randomised trial (H0648g) showing that H + CT achieves significant survival advantage over CT alone, 25 v. 20 months (with a majority of patients receiving H on relapse) [Slamon et al, NEJM 15: 783, 2001]. The converse and relevant trial of H + CT v. H followed by CT has not so far been done. However a non-randomised study of H monotherapy as first-line treatment before chemotherapy for MBC (H0650g) involving 114 women achieved a response rate of 34% in HER2 IHC 3+ patients, a median response duration of 19 months and a median survival of 24 months [Vogel et al, Proc ASCO 19: abstr 275, 2000]. 57% of these patients had received adjuvant anthracycline chemotherapy. Comparative data on IHC3+ patients randomised to H + paclitaxel (currently the recommended combination for H) in trial H0648g include a response rate of 41%, a median response duration of 10.5 months and a median survival of 25 months. 97% of these patients had likewise received adjuvant anthracyclines. These non-randomised data suggest that survival may not be impaired by using Herceptin as single-agent monotherapy before chemotherapy, with a longer response duration and potentially improved quality of life. A randomised trial is indicated, but interesting design questions are raised.

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Screening for colorectal cancer – a word in favour

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Surgery has been the mainstay of treatment of this disease for a century; improvements have centred mainly around increasing the rate of sphincter-saving in rectal cancer, and in the development of adjuvant therapies. Another important innovation in the past two decades has been the identification of sufferers presymptomatically, when surgery is likely to be much more effective; this aspiration is at the heart of population screening.

Almost nowhere has colorectal cancer screening been introduced as national policy as robust research evidence of efficacy has not been available. It has taken almost 20 years to conduct and interpret the necessary randomised control trials of faecal occult blood testing (FOBT). Data from three such trials have shown that death rates could be cut by up to 20% if governments rose to the challenge. In the UK, the government has set up pilot centres covering two million people to examine the practicalities of an FOBT based programme; these studies will be completed in 2003. Amongst other issues, this important step will check that a service of the necessary quality can be delivered, and will establish the true costs in practice.

Meanwhile the UK RCT of once-only flexible sigmoidoscopy has completed its screening phase; early data on outcomes should be available in 2003. By finding in particular those with adenomas, this approach should have a significantly bigger effect on incidence (and not just mortality) compared to FOBT. Other tests, including those identifying mutant genes in the stool of cancer patients, are under active investigation.

Identification of families with genetic predisposition to colorectal neoplasia has improved dramatically over the past decade, with molecular diagnosis moving from the research laboratory to routine practice. Better targeted colonoscopy is thus diminishing risk through prophylactic polypectomy.

Until radically new medical interventions provide opportunities to improve outcomes in symptomatic patients, screening offers the best chance for cutting substantially the death rate for colorectal cancer in the coming decade.

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Controversies in colon cancer - screening (con)

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The idea of prevention of disease, as well as early detection of cancer, is very attractive to most people. This is so especially when people are told