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.

1355

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

that screening can reduce mortality in colorectal cancer with up to 30% and also attractive to health care providers when they are told that it is cost/effective.

But, it is not that simple. There are many sources of error and bias in studies performed. This varies as in breast cancer screening where doubt now has been pronounced concerning the scientific validity of the studies, which are the basis for current recommendations (P Gøtzsche, The Lancet 2000; 355: 129–34).

Today much is focused on evidence based medicine. A firm base is especially important when you are introducing a new treatment of – as in this case – will introduce a population screening.

According to my opinion we do not have scientific data enough to advice those responsible for health care (i.e. politicians) that screening should be introduced. Especially if drawbacks ate not considered in a balanced view.

In the debate I will point out that:

(1) A relative decrease in mortality of 15–30% corresponds to an absolute reduction of less of than 0.1% and that the NNT is high (650–1250).
(2) Performed studies do not inform about number of years gained due to screening.
(3) Performed studies very seldom report, or discuss, any harm caused by screening.
(4) Cost/effectiveness is only estimated.
(5) In concluding I will claim that not only the scientific analysis must be validated but that ethical and economical considerations must be done, not at least taking the harm/benefit ratio into account

1357

Follow-up in colon cancer

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Regular follow-up programs for colorectal cancer patients are time-consuming and require a highly skilled staff. Therefore the question is often raised whether an aggressive follow-up actually helps to improve the overall results and the individual prognosis. There is no doubt that the slow growth rate of large bowel carcinomas provides a fair chance for effective surgery of a recurrent tumor. However, an intensive, varied diagnostic program, repeated at short intervals, is necessary for the detection of recurrent disease in time to permit another attempt at radical cure. In our hospital an out-patient clinic for follow-up patients was initiated. The results of aggressive follow-up were studied to assess:1) patient compliance, 2) early diagnosis of recurrent disease, 3) incidence of curative surgery for recurrence, 4) life expectancy after radical surgery for recurrence. Results of a computer-aided follow-up program for patients with colorectal cancer were analyzed. In a 10 year period 1293 patients underwent this program, the drop-out rate was 17%. 299 recurrences in 168 patients were discovered (40% local recurrence, 29% liver metastases and 31% others). 51% of patients with local recurrence and 47% with liver metastases were symptomfree. Radical surgery could be performed in 50% of local recurrences and in 26% of liver metastases. The 3 year survival rate after radical surgery was 35% for local recurrences and 33% for liver metastases, the five-year-survival rate 23% and 15%, respectively.

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Against follow-up after curative surgery for colorectal cancer

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Vast amounts of resources, human as well as economic have been utilized over many years to detect recurrence at an early stage, making it suitable for surgical removal and thereby possible prolongation of life. Five RCT's have been published since 1995, all of these being incapable of reaching a valuable conclusion.

Overall, prospective as well as retrospective data suggest a 1% survival gain by intensive follow-up.

In recent years, a prolongation of life has been demonstrated after palliative chemotherapy for recurrent colorectal cancer, when the recurrence is detected in an asymptomatic stage.

Multicenter, multinational RCT's have been suggested to assess the best follow-up, but cost calculations based on the Danish RCT show, that a small benefit from intensive follow-up (1–2% increase in long-term survival) will be at least 4 times as expensive as that obtained by initial screening of persons with average risk for colorectal cancer.

Colonoscopy should not be used for detection of recurrence, but repeated colonoscopy with polypectomy may reduce incidens as well as mortality from metachronous colorectal cancer.

References

[1] Kjeldsen BJ, Thorsen H, Whalley D, Kronborg O. Influence of follow-up on health-related quality of life after radical surgery for colorectal cancer. Scand J Gastroenterol 1999; 34: 509–15

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Decrease in prostate cancer mortality following introduction of prostate specific antigen (PSA) screening in the Federal State of Tyrol, Austria, 1993–99

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Introduction and Objectives: Several factors support the use of screening tests for early detection of prostate cancer. First, patients do not experience symptoms in the early stages, and are unlikely to seek medical attention until the disease has progressed. Second, improvements in detection methods have increased the prospect for identifying the disease at an early stage when the lesion is still organ-confined, more easily treated, and often curable.

Methods: In 1993 PSA testing was made freely available to males aged 45–75 years in the federal state of Tyrol, Austria, and a mass screening project was launched. The Tyrol is an Alpine region in the western part of Austria with 331.410 inhibitants (65.123 males between 45 and 75). Previously (1990–1993) both PSA and digital rectal examination had been used as screening tools but not within an organised programme. The screening project was performed in collaboration with general practitioners, medical examiners, urologists, and medical laboratories in the Tyrol Blood Bank of the Red Cross. Informed consent was obtained from all volunteers participating in the program. In case of elevated PSA levels the volunteers were advised to undergo further urological evaluation, while men with normal PSA levels were invited to have a repeat PSA test twelve months later. The mass screening program was provided free of charge by the health and social security services of the Federal State of Tyrol and the University Hospital of Innsbruck.

Results: In the first year (1993) 32.3% of the 65,123 males aged 45–75 years underwent screening; 68% of all men in this age range were tested at least once in the first five years of the study. The incidence of prostate cancer in the Tyrol reached a peak in 1994 and has declined since. Significant migration to lower stages and an increase in the number of organ-confined, potentially curable prostate cancers have been observed since the introduction of this screening program. However, the percentage of clinically insignificant lesions in the screened group did not increase. Morality from prostate cancer among Tyrolean men aged 40–79, which had remained constant from 1970 to 1993, has now declined, whereas in other parts of Austria the mortality rates for males in this age range have changed much less. Based on the age specific prostate cancer mortality rates in Tyrol between 1986 and 1990 there were 17 fewer prostate cancer deaths in 1997 (32% decrease), 22 deaths fewer in 1998 (42% decrease) and 18 deaths fewer in 1999 (33% decrease) than were expected. This decrease in mortality is statistically significant ($p < 0.05$).

Conclusion: The present study shows that the policy of making PSA screening freely available to the Tyrolean population and participation of a high percentage of males aged 45–75 have led to an increase in the number of organ-confined, potentially curable cancers detected as well as to a reduction in prostate cancer mortality.

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Screening may not decrease prostate cancer mortality – policy making should be delayed (until evidence from randomised studies is available)

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Screening for prostate cancer remains a controversial issue around the world. Even in the United States where screening is highly prevalent important organisations advising on the patterns of medical care have taken contrary positions. In Europe, a statement of the committee against cancer of the European Union has adopted the view given in the title of this presentation.

Fortunately, there is evidence coming from important databases in the United States and from preliminary results of studies conducted in Europe and in Canada that screening may be effective in terms of decreasing prostate cancer mortality. This evidence however is heavily debated in the epidemiological and urological community. Even if, as is also hoped