FEDERATION OF EUROPEAN CANCER SOCIETIES

PARIS
30 October - 3 November 2005

ECCO 13
the European Cancer Conference

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New options for prostate cancer

Clinical data from trials presented at the 13th European Cancer Conference (ECCO 13, 30 October–3 November, 2005, Paris, France), showed prostate cancer patients benefiting from higher doses of radiotherapy (RT), early anti-androgen intervention, maximal androgen deprivation (MAD) therapy and single agent immunotherapy.

A multi centre phase III study led by Dr J.V. Lebesque (The Netherlands Cancer Institute, Amsterdam) showed that at 5 years, freedom from failure (FFF) in prostate cancer was significantly higher in patients receiving 78 Gy RT than those receiving the standard 68 Gy dose (64% vs. 54%, $P = 0.025$). The study recruited 669 patients with stage T1b-T4N0M0 prostate cancer, who were divided into low, intermediate and high prognostic risk groups (18%, 27% and 55% of participants, respectively) and randomized to receive either 68 Gy or 78 Gy RT. Some patients (143) in the intermediate and high-risk groups also received hormonal therapy (HR).

When the treatment groups were analyzed separately it was only in intermediate-risk patients that the benefits in FFF seen with increased radiation doses were statistically significant (74% vs. 58%, $P = 0.03$). The gain in FFF for the high risk group was smaller (52% vs. 44%, $P = 0.1$), and there was no benefit in the low risk group (84% vs. 66%, $P = 0.7$). No significant differences in overall survival and freedom from clinical failure were seen between both arms.

Professor Harry Bartelink, president of Federation of European Cancer Societies and the organizer of ECCO, commented: "From this first analysis trial the standard treatment for prostate cancer should be changed to a higher radiation dose."

The Early Prostate Cancer (EPC) programme presented its third analysis data at 7.4 year follow-up on the largest ever randomized double-blind trial of patients with non-metastatic prostate cancer, investigating the efficacy of the anti-androgen drug bicalutamide.

In the EPC trial, 8113 men with localized (T1-T2, N0/Nx) or locally advanced (T3-4, any N; or any T, N+) were treated with either 150 mg bicalutamide or placebo plus standard care (RT, radical prostatectomy or watchful waiting [WW]). Results showed that in men with locally advanced prostate cancer bicalutamide improved their chance of survival by 35% ($P = 0.003$) compared to radiotherapy alone, and reduced their risk of disease progression by 31% ($P < 0.001$). No significant progression-free survival (PFS) or OS benefit was demonstrated by the addition of the drug in patients with localized disease.

Professor Peter Iversen (Rigshospitalet, Denmark), who headed the study commented: "The results provide a significant step forward and show that men with localized disease gain no significant benefit while men with locally advanced disease derive significant benefit from the addition of bicalutamide. There was minimal impact on quality of life, allowing men to remain active and retain sexual function and interest."

Dr Heather Payne, a clinical oncologist (London, UK) added that prior to this data survival advantages had only been shown for medical castration treatments. "This study gives men with locally advanced disease a welcome choice of treatment," she said.

In a separate study, effects of HT in the form of MAD, administered 3 or 6 months prior to and during RT on locally advanced non-metastatic prostate cancer (T2bc, T3 and T4; N0, M0) in 802 patients was reported by Dr James Denham and colleagues (University of Newcastle, Australia). Results showed that in comparison to RT alone, 3 months MAD significantly improved various clinical indicators including clinical disease-free survival (HR 0.66; $P < 0.001$) and freedom from salvage therapy (HR 0.71; $P = 0.024$). Greater advantages were seen with 6 months MAD, but the authors concluded further follow-up was required to better estimate survival benefits.

Lastly, Dr Celestia Higano (University of Washington, USA) presented survival data from a second phase III trial on the use of the immunotherapy agent APC8015 in patients with asymptomatic metastatic androgen-independent prostate cancer (AIPC). Similar to the results of the first trial communicated at ASCO, 2005, APC8015 showed that at 36 months, 32% of men in the APC8015 arm were alive, compared to 12% in the placebo group ($P = 0.023$). "The combined data from these trials suggest that immunotherapy might impact survival in men with AIPC. APC8015 has a favorable safety profile and future studies in patients with earlier stage disease or in combination with other agents will be of great interest," said Dr Higano.

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Combined treatments improve pancreatic cancer survival

The addition of capecitabine to gemcitabine, over gemcitabine alone, produced significant improvements in overall survival in patients with advanced pancreatic cancer and should be considered one of the new standards of care, concludes a phase III study presented in the ECCO Presidential Symposium (PS11).

Between May 2003 and January 2005, 533 patients with previously untreated or cytological proven locally advanced/metastatic carcinoma of the pancreas were randomised to receive either gemcitabine alone (GEM), or gemcitabine and capecitabine (GEM-CAP). Treatment was continued until either disease progression was seen or intolerable toxicities occurred. The primary outcome measure was survival. At the time of an interim analysis performed in May of 2005, 70% of the patients had died.

Investigators found the GEM-CAP combination significantly improved overall survival compared to GEM alone (hazard ratio 0.80; 95% CI 0.65–0.98; $P = 0.026$). The median survival for GEM alone was 6 months, compared with 7.4 months for the combination. The one-year survival rates were 19% for GEM alone and 26% for GEM-CAP.

Grade 3 or 4 toxicities for the GEM alone and GEM-CAP arms, respectively, were as follows: anaemia (2%, 1%), neutropenia (11%, 17%), thrombocytopenia (2%, 3%), fever (1%, 0%), diarrhea (1%, 1%), hand-foot syndrome (0%, 2%) and vomiting (2%, 1%). There were no reported cases of stomatitis in either group.

The trial represents the second to show an advantage for combination treatments. In May this year at the American Society of Clinical Oncology meeting (Orlando, Florida) Malcolm Moore from the Princess Margaret Hospital (Toronto, Canada) presented a study in 569 patients showing that at 1 year, 24% of those receiving erlotinib in addition to GEM were alive, compared to 17% treated with GEM and placebo.

However, at ASCO 2005 a study by the Swiss Group for Clinical Cancer Research (SAKK) in 320 patients with locally advanced/metastatic disease showed GEM plus CAP had no effect on survival compared to GEM alone.

Dr Ian Chau, one of the investigators of the current study (Royal Marsden Hospital, UK), commented: "The explanation for these differences is probably that the positive studies were better powered to show small, but clinically relevant survival advantages. In addition, the dose schedule we used was higher than the SAKK study."

He added that the combination of GEM CAP could provide a new treatment platform on which other biological and cytotoxic drugs could be added.

Herceptin shows benefits after adjuvant chemo

Results from the first and only interim analysis of the Breast International Study (BIG) show Herceptin (trastuzumab) given to HER-2 positive breast cancer patients after adjuvant chemotherapy produced significant improvements in disease free survival.

In the study , presented in the presidential symposium (abstract PS4), 5090 early breast cancer patients with HER-2 positive breast cancer, who had completed at least four cycles of neoadjuvant chemotherapy, were randomised to receive 1 year of Herceptin infusions every 3 weeks, 2 years of Herceptin infusions every three weeks or one year of observation. For women with hormone receptor positive disease, adjuvant endocrine therapy (most commonly tamoxifen) followed chemotherapy.

Results released at ECCO on the recommendation of the Independent Data Monitoring Committee, focussing solely on the 1 year Herceptin ($n = 1694$) and observation groups ($n = 1693$), showed a significant difference in disease-free survival (DFS) after a median follow-up of 12 months in favor of herceptin – 85.8% of women on herceptin were disease-free at 2 years vs. 77.4% of the observation group (hazard ratio = 0.54, $P < 0.001$).

A more detailed analysis of the site of recurrences showed herceptin reduced the risk of distant, locoregional, contralateral, and non-breast malignancies. In addition, an exploratory subgroup analysis suggested Herceptin extended DFS irrespective of age, menopausal status, nodal involvement, tumor size, and other variables.

In terms of safety, however, Herceptin-treated women were more likely to develop heart failure or a reduction in left ventricular ejection fractions. Dr Michael Untch, the principle investigator, said that all cardiac events had been manageable and reversible, with no cardiac deaths in the Herceptin group, compared to one in the observation group.

"Long-term follow-up will provide clarification of the survival gain, further safety data, and information on the optimum duration of Herceptin therapy," he concluded.

• A new monoclonal antibody, bevacizumab, for the treatment of locally advanced metastatic breast cancer had Phase III data presented. Bevacizumab is a monoclonal antibody to vascular endothelial growth factor and acts to inhibit tumour angiogenesis. In the E2100 randomized trial, the efficacy and safety of paclitaxel with or without bevacizumab was assessed as first-line therapy in 722 patients with locally advanced or metastatic breast cancer. Combination therapy increased response in all patients (28.2% vs. 14.2%; $P < 0.0001$) and in those with measurable disease (34.3% vs. 16.4%; $P < 0.0001$). Progression-free survival (PFS) was also improved in the bevacizumab arm relative to paclitaxel alone (10.97 vs. 6.11 months; HR 0.498; $P < 0.001$).

Dr Kathy Miller (Indiana University Cancer Centre, USA), lead author, said: "Importantly, the improvements in response rate and PFS were obtained with minimal increase in side effects. Given the benefit of bevacizumab in patients with metastatic disease, we look forward to initiating trials in the adjuvant setting".