5019 POSTER DISCUSSION

Discordant Treatment Effects According to Menopausal Status Following Adjuvant Zoledronic Acid in Stage II/III Breast Cancer − The AZURE Trial (BIG 01/04)

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Background: The AZURE trial is an academic study designed to determine whether zoledronic acid (ZOL) added to standard adjuvant therapy reduces the risk of recurrence and improves survival in patients with stage II/III breast cancer.
Materials and Methods: 3360 patients from 174 centres were randomized to receive (neo) adjuvant chemotherapy (CT) and/or endocrine therapy +/− ZOL 4 mg iv every 3−4 weeks for 6 doses, then 3 monthly $\times$ 8 and 6 monthly $\times$ 5 to complete 5 years treatment. A second interim analysis with boundaries set for both efficacy (HR 0.833, alpha spend 1%) and lack of clinical benefit (HR 0.936 with a 5% risk of declaring a false negative result) recently resulted in release of data after the boundary for the latter was crossed.
Results: Patient and treatment characteristics were well balanced. 3208 patients (96%) received (neo) adjuvant CT. With a median follow-up of 59 (IQR 53.2–60.9) months, there have been 807 invasive disease free survival (IDFS) events. ZOL had no overall effect on IDFS (adjusted H.R. 0.98, 95% CI 0.85–1.12; p = 0.73). To date, 519 deaths have occurred, 276 control and 243 ZOL (adjusted HR = 0.85; 95% CI 0.72, 1.01, p = 0.07). Pre-specified subgroup analyses showed consistent lack of effect across the minimisation criteria other than for menopausal status. Here, significant heterogeneity of treatment effect ($chi^2_1 = 7.91$; p = 0.0049) on IDFS was observed between those who were >5 years post-menopause (n = 1041; adjusted HR = 0.75; 95% CI 0.59–0.96, p = 0.02) and all other (pre, peri and unknown status) menopausal groups (n = 2318; adjusted HR = 1.15; 95% CI 0.97–1.36, p = 0.11). This was due to a profound treatment interaction difference in first extra-skeletal IDFS events between the two menopausal groups ($chi^2_1 = 14.00$, p = 0.0002) rather than first recurrence in bone ($chi^2_1 = 0.14$, p = 0.70). Treatment effects were independent of ER status, tumour stage and lymph node involvement. In the established postmenopausal subgroup, a significant improvement in overall survival was seen (adjusted HR = 0.74; 95% CI 0.55–0.98, p = 0.04).
Conclusions: The results do not support the routine use of adjuvant ZOL in unselected patients with early breast cancer. However, the remarkable heterogeneity of treatment effect by menopausal status merits further study into the underlying mechanisms affecting extra-skeletal recurrence rates, and suggests a potential role for ZOL in women with established postmenopausal levels of reproductive hormones at diagnosis.

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KORTUC II − a New Image-Guided, Enzyme-Targeted, and Breast Cancer Stem Cell-targeted Chemo-radiosensitization Treatment for Patients With Locally Advanced Breast Cancer

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Background: Tumour tissue can be re-oxygenated by inactivating peroxidase/catalase through application of hydrogen peroxide (H_2O_2), which is degraded to produce oxygen. In this way, low LET- radioresistant tumours can be transformed into radiosensitive ones. The purpose of the present study was to establish a non-surgical treatment strategy for patients with locally advanced breast cancer (LABC) by utilizing a novel Kochi oxydol-radiation therapy (RT) to induce radiosensitization in unresectable carcinomas (KORTUC).
Materials and Methods: A new radiosensitizing agent containing H_2O_2 and sodium hyaluronate was developed for intra-tumoral injection. The agent is composed of 0.5% H_2O_2 and 0.83% sodium hyaluronate (CD44). Our local ethics committee approved the use of this new method, called KORTUC II, for treatment of breast cancers and metastatic lymph nodes. A total of 16 patients with LABC were enrolled to receive KORTUC II with systemic chemotherapy (CT) after providing informed consent. Patients underwent induction CT followed by KORTUC II radiosensitization treatment and adjuvant CT (after RT). Endocrine therapy was also used in cases of estrogen or progesterone receptor-positivity. A maximum of 6 ml of the agent was injected into breast tumour tissue twice a week under ultrasound (US) guidance, just prior to administration of RT, beginning with the sixth fraction of RT. The agent was also injected just prior to the fifth and sixth cycles of EC (epirubicin/cyclophosphamide) CT in patients who had a poor response to the first four cycles of EC. In regards to RT, hypofraction RT was given using a tangential field approach; the energy level was 4 MV, and the total RT dose was 49.5 Gy administered as 2.75 Gy/fraction.
Results: Treatment was well tolerated with only minimal adverse effects in all 16 patients. A total of 13 patients achieved clinical complete response, and one patient achieved a clinical partial response (cPR). Another two patients underwent surgical resection following induction CT with KORTUC II. Patients did not show any significant complications (with the exception of mild dermatitis), and cosmetic results were excellent for nine patients. The mean follow-up period at the end of February 2011 was 33.8 months, at which time only one patient who showed cPR and refused any treatment thereafter had died; the other 15 patients were alive without any distant metastases. Only one patient had liver metastasis, which was detected at 18 months after treatment and which was controlled by intra-arterial CT.
Conclusions: Non-surgical care for LABC can be performed with KORTUC II chemo-radiosensitization treatment. KORTUC II has four major characteristics: US-guided administration, enzyme-targeting of peroxidase/catalase, enhancement of the therapeutic effects of EC CT, and targeting of breast cancer stem cells via CD44. These data suggest that KORTUC II is a viable and noninvasive replacement for surgery and is a valuable radiosensitization strategy for radioresistant neoplasms.

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Multivariable Prognostic Model for Individual Survival Prediction of Metastatic Breast Cancer Patients Taking Into Account Circulating Tumour Cells (CTC) Count Before and During Chemotherapy

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Background: CTC count at baseline, and CTC count changes before cycle 2 recently became a validated independent prognostic marker in metastatic breast cancer. We created a prognostic tool which takes into account for the accurate prediction of progression-free survival (PFS) and overall survival (OS).
Methods: Data from the IC 2006−04 study were used. This prospective multicentre study included 267 metastatic breast cancer patients treated by first line chemotherapy with or without targeted therapy, in whom appropriate pre-treatment prognostic variables (age, performance status, number of metastatic sites, disease-free interval, ER, PR and HER2 status, tumour grade, LDH, serum markers, CTC count by CellSearch technique before treatment and before cycle 2) were available for statistical analysis. We constructed a multivariate Cox regression model for PFS and OS prediction. A stepwise selection process was applied to achieve the most informative and parsimonious models. Performance was measured with the C-index statistic. Internal validation was performed using leave-two-out technique.
Results: Four nomograms have been obtained, in two clinical settings: at inclusion (before the start of any treatment) taking into account the initial CTC count, and during treatment (before cycle 2) taking into account CTC changes under treatment. Their accuracy was good for PFS and OS prediction, with C-index ranging from 0.72 to 0.88. Internal validations allow considering a good accuracy of the models in an external population.
Conclusion: These clinically relevant nomograms are a simple tool for a personalized prognostic assessment including CTC assessment.