minimize side effects became more important. To reduce the dose to lung and heart in the case of chest wall irradiation using an appositional electron beam, we used an individualized custom bolus which was accurately designed to compensate the difference of chest wall thickness. The benefits were evaluated by comparing the normal tissue complication probabilities (NTCPs) and dose statistics with boluses to those without boluses.

Methods: Boluses were made and the effects were evaluated for ten patients treated with the reverse hockey stick technique. Electron beam energy was determined in order to irradiate 80% of the prescription dose to the deepest lung-chest wall boarder, which was usually located at the internal mammary lymph node chain. An individualized custom bolus was made to compensate the chest wall thinner than the prescription depth by accurately measuring the chest wall thickness at 1cm2 interval on the planning CT images. Second planning CT was obtained overlying the individualized custom bolus to each patients' chest wall. 3-D treatment planning was performed using ADAC-Pinnacle3 for each patient with or without bolus. NTCPs based on "the Lyman-Kutcher" model were analyzed and the mean, maximum and minimum doses for heart and lung were computed.

Results: The average NTCPs in the ipsilateral lung were reduced from 80.2 ± 3.43% to 47.7 ± 4.61% when individualized custom boluses were used, which shows statistically meaningful reduction ($p < 0.01$). The mean lung dose also was reduced about 430 cGy from 2757 cGy to 2327 cGy. The reduction of NTCP and the mean lung dose appeared to have statistically meaningful correlation since 'p value' was < 0.01. The NTCP in the contralateral lung as well as the heart were 0% even in the case of no bolus due to the small effective radiation volumes, mean value 4.4% and 7.1% respectively.

Conclusion: The use of an individualized custom bolus in the radiotherapy of postmastectomy chest wall reduce the NTCP of ipsilateral lung about 30-35%, which can increase the complication free cure probability of breast cancer patients.

690 POSTER

Salvage peroperative hdr or PDR brachytherapy for chest wall or infraclavicular recurrence of breast cancer in post mastectomy patients - a feasibility study

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Introduction: For patients with a local recurrence of post mastectomy breast cancer after external beam radiation (EBRT), we investigated the feasibility of fractionated salvage HDR or PDR brachytherapy (BT).

Material and methods: Thirteen patients with a local recurrence after EBRT and 1 patient without previous EBRT were treated between 1996 - 2000 in the age of 37 -85 years (mean 59 years). For 11 patients it was the second or third local recurrence. The mean previous EBRT dose was 58 Gy (range 42 - 62 Gy) and the mean EBRT- BT interval was 42 months. Local recurrence was resected and the tumor bed was marked with surgical clips. Mean 7 plastic tubes were implanted to the target during the surgery. After CT based 3D inverse BT planning a mean dose of 29 Gy (10 -40 Gy) was applied to the target shaped reference isodose. Two patients received additional EBRT (40 and 50 Gy).

Results: After a mean follow up of 12 months (range 1-33 months) we observed 7 out of 14 patients without signs of local progress or recurrence. Seven patients had a local recurrence or progress after a mean interval of 6 months (range1-18 months). However, in 8 out of 14 cases we observed later a systemic progress. No RTOG III or IV side effects were developed. All 7 patients with a local control have a good cosmesis.

Conclusions: For patients with local recurrences in previous irradiated field salvage peroperative Brachytherapy seems to be offering a meaningful chance for local control and/or better quality of life.

Metastatic breast cancer

691 POSTER

Health-related quality of life (HRQL) in women with HER2-positive metastatic breast cancer: effect of treatment with trastuzumab (Herceptin) plus chemotherapy versus chemotherapy alone

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Purpose: The addition of Herceptin (H) to chemotherapy (CT) produces significant benefits in women with HER2-positive metastatic breast cancer (MBC), including a survival advantage (Slamon DJ et al, NEJM 2001;344:783). We have reported previously that HRQL is stable in women treated with H monotherapy and improves in those who respond (Cobleigh MA et al. JCO 1999;17:2639). HRQL generally worsens in women treated with CT. We have compared HRQL in patients with HER2-positive MBC treated with H+CT or CT alone in a pivotal phase III trial.

Methods: The pivotal trial included 469 patients, of whom 400 completed an HRQL questionnaire (EORTC QLQ-C30) at baseline and on one or more subsequent occasions at 8, 20, 32, 44 and 56 weeks. These 400 patients had been randomized to receive either H+CT (208 pts) or CT alone (192 pts). CT consisted of either doxorubicin (epirubicin in 36 women) and cyclophosphamide or paclitaxel. HRQL improvement or worsening were defined as a >/=10 change in scores (range 0-100) from baseline in each of 6 preselected domains: global QL, physical, role, social, and emotional functioning, and fatigue. Changes of <10 were defined as stable HRQL.

Results: Baseline scores were similar in the H+CT and CT groups. At 32 weeks, global QL, physical functioning and fatigue showed statistically significant improvement ($P<0.05$) over baseline scores in the H+CT group. In contrast, scores in these domains deteriorated in the CT group. Statistically significantly higher proportions of patients in the H+CT group reported improvement in global QL (51 vs. 36%, p=0.003) and in fatigue (52 vs. 42%, p=0.03) than in the CT alone group. Higher proportions of patients in the H+CT group also reported improvement in physical (37 vs. 29%, p=0.08) and role functioning (29 vs. 21%, P=0.08), but these were not statistically significant. Interestingly, the proportions of patients in the two groups that reported worsening were similar, but significantly fewer patients in the H+CT than in the C group had stable scores for global QL (9 vs. 21%, P=0.0003) and social functioning (11 vs. 19%, P=0.03).

Conclusions: The addition of H to CT did not cause the proportion of patients reporting worsening HRQL to increase. In contrast, significantly more patients experienced improvements in global QL and fatigue when treated with H+CT than when treated with CT alone. (Supported by Genentech, Inc.)

692 POSTER

Older (age >60 years) patients obtain survival benefit from herceptin plus chemotherapy

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Background: Entry to the pivotal phase III trial that demonstrated that adding Herceptin (H) to chemotherapy (C) (doxorubicin/epirubicin and cyclophosphamide [AC] or paclitaxel [T]) as first-line therapy for HER2-positive metastatic breast cancer (MBC) improves response rate (RR) (50% versus 38%, p=0.003) and survival (odds ratio, 0.80, p=0.046) was not restricted by age. Methods: We conducted a retrospective exploratory analysis to determine the influence of age on clinical benefit from H in this trial. Results: Of the 469 patients enrolled in the pivotal phase III trial, 360 (77%) were aged <60 years and 109 (23%) >60 years. Although baseline patient characteristics were similar between the 2 groups, patients aged >60 years had a worse baseline Karnofsky Performance Status (score <80, 41% vs 30%), higher initial nodal burden (>4, 52% vs 34%), longer disease-free interval from adjuvant therapy (26 vs 20 months), more frequent prior exposure to hormonal therapy (71% vs. 54%), and less frequent adjuvant exposure to anthracyclines (31% vs. 40%). Outcomes are shown below.

Response rate (<60 years): C alone, 33%; H + C, 52%
Response rate (>60 years): C alone, 28%; H + C, 44%
Survival (<60 years): C alone, 23 months; H + C 26 months
Survival (>60 years): C alone, 24 months; H + C 19 months

The survival benefit obtained by adding H to C in patients aged >60 years was statistically significant (odds ratio: 0.64 95% CI: 0.41-0.99).

These survival benefits were observed even though the study design resulted in 65% of control patients receiving H at disease progression. Cardiac dysfunction (CD) in the H + T arms occurred in 11% of patients aged <60 years and 21% of those aged >60 years. All CD events in those aged >60 years improved to grade 1 with treatment and H was continued. Conclusions: Patients with HER2-positive MBC who are more than 60 years of age appear to have a worse overall outcome than patients aged <60 years. This could be related to poor baseline prognostic characteristics. However, the survival benefit due to the addition of H to C in the older age group was significant. These data indicate that there is no reason to withhold first-line H + C therapy in older (age >60 years) patients with MBC.

693 POSTER

Capecitabine (Xeloda) in 162 patients with paclitaxel-pretreated mbc: updated results and analysis of dose modification

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Background: Capecitabine, a novel, oral, thymidine phosphorylase (TP)-activated fluoropyrimidine, exploits the high activity of TP in tumor cells to generate 5-FU preferentially at the tumor site. In the pivotal trial evaluating capecitabine in 162 heavily pretreated MBC patients, the response rate was 20% (29% in a subgroup of 42 patients resistant to both doxorubicin and paclitaxel), median time to progression (TTP) was 3.0 months and median overall survival (OS) was 12.8 months [Blum et al, JCO 1999]. Myelosuppression and alopecia were rare. We report updated results of this trial and an analysis of the impact of dose modification on efficacy.

Methods: 162 patients received capecitabine 1,250mg/m2 twice daily, days 1-14 every 21 days. The standard capecitabine dose modification scheme was applied if patients experienced grade 2 or more severe toxicities. A retrospective analysis was conducted to evaluate the impact of dose modification on efficacy.

Results: Median OS after 143 events is 11.6 months. Median TTP is 3.0 months. 54 patients (33%) required capecitabine dose reduction for adverse events. The dose was reduced to 75% of the starting dose after a median of 1.6 months in 45/162 patients (27%). A retrospective analysis demonstrated that patients requiring dose reduction for adverse events experienced no significant increase in risk of progression (hazard ratio 1.07, Wald test p=0.73) compared with those not requiring dose reduction.

Conclusions: Capecitabine monotherapy has shown considerable activity in heavily pretreated MBC. Dose modification from the standard starting dose to each patient's individually tolerable dose does not reduce efficacy. Given these results, capecitabine at a starting dose of 1,250mg/m2 twice daily, days 1-14, should be considered the reference treatment for patients whose disease has progressed with prior taxane therapy.

694 POSTER

Relationship of estrogen receptor (ER) status to clinical benefit in clinical trials of herceptin

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Background: HER2 proto-oncogene amplification and/or HER2 receptor overexpression is associated with poor prognosis in breast cancer. It has been reported that there is an inverse correlation between HER2 receptor levels and ER levels. It has also been suggested that targeting HER2 using Herceptin (H) may restore sensitivity to hormonal therapy in patients who have developed resistance. Therefore, we analysed the relationship of ER status to outcomes in the pivotal H trials and a trial of first-line H monotherapy. These trials demonstrated that H monotherapy is active as first- and second-line therapy for metastatic breast cancer and that H plus chemotherapy significantly improves survival. Methods: 805 HER2-positive patients (2+/3+ by IHC) were enrolled in these three clinical trials. A retrospective analysis was undertaken to compare the outcomes of ER+ and ER- patients treated with H. Tumors positive for the progesterone receptor (PR) respond to hormone therapy similarly to tumors that are ER+; therefore, ER-/PR+ tumors are included with ER+ tumors for the purpose of this analysis. Results: 50% of the 805 patients enrolled were ER+, 40% were ER-, and 10% were ER unknown. Outcomes are shown below.

First-line monotherapy (ER+ vs ER-): RR, 25 vs 29%; TTP, 3.8 vs 3.4 months; survival, 26 vs 20 months

Second/third-line monotherapy (ER+ vs ER-): RR, 16 vs 16%; TTP, 3.2 vs 3.0 months; survival, 14.2 vs 12.4 months

H + chemotherapy (ER+ vs ER-): RR, 53 vs 49%; TTP, 6.6 vs 7.0 months; survival, 25.4 vs 24.1 months

Conclusions: The above data support the conclusion that ER-/HER2+ patients and ER+/HER2+ patients have similar clinical outcomes when treated with H alone or H + chemotherapy. Therefore, ER status should not preclude testing for HER2 status and does not predict benefit from H in HER2+ patients.

695 POSTER

Results of two open label Multicentre phase II pilot studies with Herceptin in combination with docetaxel and platinum salts (Cis or Carboplatin) (TCH) as Therapy for Advanced Breast Cancer (ABC) in women with tumors over-expressing the HER2-neu proto-oncogene

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Preclinical data indicate that docetaxel (T) and/or platinum salts (C) are highly synergistic with Herceptin (H). This synergy, taken together with the activity of these drugs in ABC, and the need to develop non-anthracycline containing regimens with H, led to our performing two pilot studies to evaluate the safety and efficacy of T and H in combination with cisplatin (TCisH) or carboplatin (TCarboH). Both studies enrolled ABC patients whose tumors were positive for the HER2 alteration by immunohistochemistry (IHC) or fluorescent in-situ hybridization (FISH), with retrospective analysis by FISH planned on all primary tumors. T (75 mg/m2) and C (cis 75mg/m2, Carbo, AUC of 6) were given on day 1, and then q3wks up to 8 cycles. H was given on day 1 cycle 1 (4mg/kg) then continued weekly at 2mg/kg for 1 year or until progression.

Results: Enrollment is complete with 61 TCisH pts and 60 TCarboH pts. Interim results are on 34 TCisH pts (162 cycles) and 27 TCarboH pts (159 cycles). Pt characteristics for TCisH and TCarboH respectively were: prior adj chemo 56% and 67%, visceral mets 76% and 78%, liver mets 38% and 26%, lung mets 35% and 56%, bone mets 44% and 41%, and 3 or more organs involved 32% and 26%. Febrile neutropenia was 9% on TCisH and 11% on TCarboH, there was one grade 3 infection on TCarboH. G3-4 non-hematological toxicities for TCisH and TCarboH respectively were: nausea 12% and 7%, vomiting 6% and 4%, diarrhea 9% and 4%, stomatitis 3% and 11%, and neurosensory 3% and 0%. There were no G3-4 renal or ototoxicities. Grade 1-2 ototoxicities were seen in 18% of TCisH pts. One pt in each study developed CHF (1 prior cardiac history). Responses were seen in 26/34 (3 CRs, 23 PRs, ORR 76%) of TCisH pts HER2 positive by IHC, and in 10/14 (3 CRs, 7 PRs, ORR 71%) TCarboH patients HER2 positive by FISH.

Conclusion: These pilot studies show that the TCH combinations are feasible and are active in ABC, and justify their study in random assignment trials. BCIRG is conducting such studies in both the metastatic and adjuvant settings. Final results for all patients will be presented.

696 POSTER

Fractionated half'body irradiation (HBI) for widespread bone metastases (WSBM) from breast cancer: A randomized phase III trial of the international atomic energy agency (IAEA)

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Purpose: Find the fastest and most effective method to economically deliver fractionated HBI for WSBM from breast cancer.

Methods: Phase III trial with 3 arms for WSBM: (A) Control-Convent, daily fract. (15 Gy/5 fx/5 days); (B) Hyperfract. (8 Gy/2 fx/1 d); (C) Accel. Fract. (12 Gy/4 fx/2 d). Of 156 pts. entered, 72 (46%) had breast cancer primaries; 27, 25 and 20 pts. were random. to arms (A), (B) & (C) and constitute the subject of this analysis. All pts had initial and subseq. pain &