enhance their experience, improve carer involvement and may enhance patient outcomes.

Sarcoma

Tuesday 27 September 2011, 09:00−11:30

30LBA LATE BREAKING ABSTRACT

A Randomized Clinical Trial of Adjuvant Chemotherapy with Doxorubicin, Ifosfamide, and Cisplatin in Localized Uterine Sarcomas. Results On 81 Randomized Patients

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Background: Uterine sarcomas (US) have a high risk of metastatic relapse. No benefit was shown with doxorubicin as adjuvant treatment even though a trend emerged in favor of chemotherapy (CT) (Omura 1985). A multichemotherapy approach in US achieved a good response rate (DECAV therapy: 54% overall response rate), though toxic. Adjuvant API (doxorubicin, ifosfamide and cisplatin) followed by radiotherapy (RT) is a feasible protocol. We conducted a phase III multicenter study of adjuvant CT with API. The objective was to detect an increase $\geqslant$20% of 3 years PFS (a = 5%, power = 80%) in the CT arm. Study was stopped because of lack of recruitment. We present the results of the 81 pts who actually entered the study.

Material and Methods: Pts with FIGO stage $\leqslant$III US after complet surgery, normal thoracic, abdominal and pelvic CT scan, physiological age $\leqslant$65 years, PS $\leqslant$ 2, left ventricular ejection fraction >50%, were randomized (stratification carcinosarcomas [CS] versus others). All patients received pelvic RT (45 grays); vaginal brachytherapy was optional. Chemotherapy consisted in 4 cycles of doxorubicin 50 mg/m^2 d1, ifosfamide 3 g/m^2/d d1d2 + mesna, cisplatin 75 mg/m^2 d3, + lenograstim 150 μg/m^2/d d 7−14; q 3 wks.

Results: 81 patients randomized, 39 in arm A (CT + RT) and 42 in arm B (RT); median age 55 y (39−69), 52 stage I, 16 stage II, 13 stage III; 53 leiomyosarcomas, 9 indifferenciated sarcomas, 19 CS. Gr 3−4 toxicity during API (/37 pts): hematologic gr3 (16%) and 4 (68%); febrile neutropenia (22%) with 2 toxic deaths; renal gr 4 (1 pt); nausea-vomiting gr 3−4 (24%); 28% of pts needed dose reduction. With median follow-up of 4.3 years, 41/81 pts recurred at a median time of 13 mo (5−43 mo), 15 in arm A (38%) and 26 in arm B (62%); median DFS is 33 mo; recurrences sites was: pelvis 11, pelvis + meta 3, meta 27 (25/30 meta: lung). 3 years DFS is 55% in arm A (IC95: 40−70) and 41% in arm B (IC95: 27−57) p = 0.048. 3 years OS is 81% in arm A (IC95: 66−91) and 69% in arm B (IC95: 52−82) NS.

Conclusions: With median follow-up of 4.3 years, API adjuvant chemotherapy increases statistically the 3 year-DFS of patients with uterine sarcoma.. Results have to be confirmed with longer follow-up to see real impact on OS. The 2 toxic deaths may impact the global prognosis. A selection of less toxic chemotherapy is mandatory.

Sarcoma

Tuesday 27 September 2011, 09:00−11:30

31LBA LATE BREAKING ABSTRACT

Response to Imatinib Rechallenge of GIST That Recurs Following Completion of Adjuvant Imatinib Treatment − the First Analysis in the SSGXVIII/AIO Trial Patient Population

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Background: Adjuvant imatinib improves outcome of patients with operable GIST, but many GISTs recur after completion of adjuvant therapy. Efficacy of imatinib in recurrent GIST following adjuvant treatment is unknown, and concern has been expressed that prior exposure to imatinib may reduce efficacy of the drug in the advanced setting. The SSGXVIII/AIO trial recruited patients with KIT-positive GIST, estimated to have a high risk of tumor recurrence based on the modified NIH Consensus Classification from February 2004 to September 2008.

Patients and Methods: The intention-to-treat population consisted of 397 patients, of whom 199 were randomly assigned to receive 12 months of imatinib and 198 36 months of imatinib. Imatinib was administered orally at a dose of 400 mg/d in both groups. The patients were monitored with computed tomography at 6-month intervals during follow-up. With a median follow-up time of 54 months, 84 and 50 patients were diagnosed with recurrent GIST or died in the 1-year and 3-years groups, respectively. Patients who did not have GIST at central pathology review (n = 15) and those with metastatic GIST at the time of randomization (n = 24) were excluded from the current analysis.

Results: Eighty-one patients were treated with imatinib for recurred GIST (1-year group, 54; 3-years group, 27). Forty-six (56.8%) out of the 81 patients were evaluable for response (6 were not evaluable, and 29 had missing data or were too early for evaluation). Imatinib was administered at a dose of 400 mg/d for 71 patients (87.7%). The remaining 10 patients received 100 mg (n = 3), 600 mg (n = 1) or 800 mg (n = 6), respectively. Fifteen (32.6%) patients achieved a CR, 14 (30.4%) a PR, 10 (21.7%) had SD and 7 (15.2%) PD as the best response yielding a clinical benefit rate CBR (CR + PR + SD) of 84.8%. There was no difference in the CBR between patients assigned to the 1-year and 3-years groups (87.9% vs. 76.9%, respectively; p = 0.385). The median time to progression after starting imatinib for advanced GIST was 35.7 months (1-year group: 39.6 months; 3-year group: 20.8 months; HR 1.60, 95% CI, 0.67–3.85; p = 0.289).

Conclusions: Most patients diagnosed with recurrent GIST after having received imatinib in the adjuvant setting respond to imatinib. The CR rate observed was high, possibly due to early detection of recurrent disease during follow-up. The observed median time to disease progression appears similar to the times found in patient populations that have not been exposed to imatinib in the adjuvant setting.

Sarcoma

Tuesday 27 September 2011, 09:00−11:30

32LBA LATE BREAKING ABSTRACT

Denosumab Treatment for Giant Cell Tumor of Bone (GCTB) in Adolescent Patients: Interim Results From a Phase II Study

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Background: GCTB is characterized by RANKL-mediated bone destruction. Symptoms include localized tenderness, swelling, fractures, and often severe, intractable pain. In a previous phase 2 GCTB study, 86% of patients had a response to the RANKL inhibitor denosumab, as demonstrated by an elimination of $\geqslant$90% of giant cells or no radiological progression of the target lesion. We report data from a preplanned interim analysis of a 2nd phase 2 study, describing denosumab effects on the adolescent subset of patients with GCTB (Amgen, Inc. ClinicalTrials.gov identifier NCT00680992).

Materials and Methods: Skeletally mature adolescent patients with surgically unsalvageable GCTB (Cohort 1, n = 8) or salvageable GCTB (Cohort 2, n = 2), $\geqslant$12 to <18 years of age, received subcutaneous denosumab 120 mg every 4 weeks with additional doses on days 8 and 15. The primary objective was to evaluate denosumab safety. We also analyzed investigators' assessments of disease progression and the proportion of patients for whom surgery was delayed, reduced in scope, or no longer deemed required. Safety analyses included all patients who received denosumab; efficacy analyses included patients who received $\geqslant$1 dose of denosumab and had the opportunity to be on study for $\geqslant$6 months. Pain was evaluated in patients who had $\geqslant$1 post-baseline pain assessment (Brief Pain Inventory-Short Form [BPI-SF] 0: no pain − 10: pain as bad as can be imagined). The BPI-SF was administered at baseline and before each dose. Analgesic use was quantified using the 8-point Analgesic Quantification Algorithm (AQA 0: no analgesics − 7: strong opioids with >600 mg oral morphine equivalent per day).

Results: Patients included 2 males and 8 females (mean age 15.6 years, range 13−17) who were on denosumab treatment for a median of 9.0 months (range 3.3–17.3). All patients had skeletal lesions. Adverse

events (AEs) were reported in 8/10 patients; none were serious. The most common AE was headache (n = 5). Six of 10 patients met the criteria for efficacy analysis. For Cohort 1 (n = 5), no patients had disease progression and 3/5 reported clinical benefit (best response: 3 reported pain reduction, 2 each reported improved mobility and function). In 9 of 12 study visits, ⩾50% of patients had a clinically meaningful improvement in worst pain (⩾2-point decrease) from baseline. Except for one patient at weeks 25 and 37, no other patient increased analgesic use from no/low (0−2 points) at baseline to strong opioids (⩾3 points) throughout the study. The one patient in Cohort 2 eligible for efficacy analysis, delayed a planned morbid surgery for at least 6 months.

Conclusions: Denosumab was well tolerated in these adolescent patients with GCTB. Reduced disease progression, delayed surgery, and clinical benefit were reported. Denosumab continues to be studied as a potential treatment for skeletally mature adolescents with GCTB.

Personalized Medicine

Sunday 25 September 2011, 09:00−10:50

33LBA LATE BREAKING ABSTRACT

Evaluation of Individual Codon 12 and 13 Mutant (MT) KRAS Alleles as Prognostic and Predictive Biomarkers of Response to Panitumumab (pmab) in Patients with Metastatic Colorectal Cancer (mCRC)

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Background: Pmab is a fully human monoclonal antibody targeting the epidermal growth factor receptor (EGFR). Significant improvement in progression-free survival (PFS) was observed in patients with wild-type (WT) *KRAS* mCRC receiving pmab + FOLFOX4 for 1st-line therapy (study 20050203; Identifier: NCT00364013; Sponsor: Amgen), pmab + FOLFIRI for 2nd-line therapy (study 20050181; Identifier: NCT00339183; Sponsor: Amgen), and pmab + best supportive care (BSC [study 20020408; Identifier: NCT00113763; Sponsor: Amgen]). Collectively, MT *KRAS* codon 12 and 13 alleles are established biomarkers for lack of response to anti-EGFR antibodies in mCRC. We evaluated the prognostic and predictive impact of individual codon 12 and 13 *KRAS* mutations in these three phase 3 studies.

Methods: Patients were randomized 1:1 to receive FOLFOX4, FOLFIRI, or BSC +/− pmab 6.0 mg/kg Q2W. The primary endpoint in studies 20050203 and 20020408 was PFS; overall survival (OS) was a secondary endpoint. In study 20050181, the co-primary endpoints were PFS and OS. *KRAS* status was determined using the Therascreen® *K-RAS* Mutation Kit (Qiagen) that detects the seven most common *KRAS* mutations in codons 12 and 13 (*KRAS* G12A, G12C, G12D, G12R, G12S, G12V, G13D).

Results: *KRAS* ascertainment rates were 93%, 91%, and 92% in studies 20050203, 20050181, and 20050408, respectively. MT *KRAS* codon 12 and 13 alleles were detected in 40% (440/1,096), 45% (486/1,083), and 43% (184/427) of tumors from patients in studies 20050203, 20050181, and 20020408, respectively. The distribution of MT *KRAS* alleles was conserved across studies, equally balanced between treatment arms, and consistent with published mCRC *KRAS* mutation analyses. Baseline demographic and clinical features were generally balanced in all MT *KRAS* allele subgroups. Across three studies, none of the individual MT *KRAS* alleles were consistently associated with PFS or OS outcomes in the treatment arms. Only in study 20050203 were two individual *KRAS* MT alleles significantly associated with outcomes: G12V was favorably and G13D was unfavorably associated with OS in the pmab-containing arm. Response rates were comparable across all MT *KRAS* allele subgroups within each of the 1st- and 2nd-line mCRC trials; no patients with MT *KRAS* mCRC responded to pmab therapy in study 20020408.

Conclusions: These retrospective analyses indicate that patients with mCRC whose tumors harbor MT *KRAS* codon 12 or 13 alleles are unlikely to benefit from panitumumab therapy. Therefore, only patients with WT *KRAS* tumors should be treated with panitumumab therapy.

Lung Cancer − Metastatic

Saturday 24 September 2011, 11:15−14:05

34LBA LATE BREAKING ABSTRACT

AVAPERL (MO22089): Final Efficacy Outcomes for Patients (pts) With Advanced Non-squamous Non-small Cell Lung Cancer (nsNSCLC) Randomised to Continuation Maintenance (mtc) with Bevacizumab (bev) or Bev + Pemetrexed (pem) After First-line (1L) Bev–cisplatin (cis)–pem Treatment (Tx)

F. Barlesi[1], J. de Castro[2], V. Dvornichenko[3], J.H. Kim[4], A. Pazzola[5], A. Rittmeyer[6], A. Vikström[7], L. Mitchell[8], E.K. Wong[8], V. Gorbunova[9]. *[1]University of Méditerranée-Assistance Publique Hôpitaux de Marseille, Multidisciplinary Oncology and Therapeutic Innovations Department, Marseille, France; [2]La Paz University Hospital, Medical Oncology Service, Madrid, Spain; [3]SIHS Irkutsk Regional Oncology Center, Department of Oncology, Irkutsk, Russian Federation; [4]Yonsei Cancer Center, Department of Oncology, Seoul, Korea; [5]Medical Oncology Hospital SS Annunziata, Oncology Service, Sassari, Italy; [6]Lungenfachklinik Immenhausen, Department of Oncology, Immenhausen, Germany; [7]The University Hospital, Department of Pulmonary Medicine, Linkoping, Sweden; [8]F. Hoffmann-La Roche Ltd, Global Medical Affairs Department, Basel, Switzerland; [9]N.N. Blokhin Cancer Research Center of Russia, Department of Oncology and Hematology, Moscow, Russian Federation*

Background: 1L bev-based Tx followed by mtc bev offers clinical benefit over chemotherapy alone, as does 1L cis–pem followed by mtc pem. AVAPERL (NCT 00961415) is a randomized, multicenter, open-label phase III study investigating whether continuation mtc with bev+pem offers benefit over bev alone after 1L bev–cis–pem. AVAPERL is ongoing and sponsored by F. Hoffmann-La Roche Ltd.

Materials and Methods: Eligible pts with advanced/metastatic/recurrent nsNSCLC who achieved CR/PR/SD after 1L bev–cis–pem were randomized 1:1 to receive bev or bev+pem until disease progression (PD) or unacceptable toxicity. Primary endpoint was progression-free survival (PFS) from start of 1L Tx to 1st PD or death from any cause. Treatment difference in PFS was evaluated by stratified log-rank test; stratification factors were gender, smoking status and response after 1L Tx. Secondary efficacy endpoints included overall survival (OS), best overall response rate (ORR), duration of response, and duration of disease control. The total analysis population included all eligible patients. The mtc analysis population included all patients randomised to receive mtc Tx.

Results: Eighty-one sites in 11 countries enrolled 376 patients between 08/09 and 07/10. Of these, 253 pts (67%) were randomised: 125 (49%) to bev, and 128 (51%) to bev+pem. Baseline characteristics were well-balanced. Tx was well-tolerated (ECCO 2011, #9.112) and QoL did not deteriorate with mtc Tx (ECCO 2011, #9.076). Median follow-up for the mtc arms was 11 mo. Data are presented in Table 1.

Table 1

	Bev mtc n = 125	Bev+pem mtc n = 128	HR	p
mPFS* (mo) (95% CI)	6.6 (6.0−7.8)	10.2 (9.1–11.7)	0.50	<0.001
mOS (mo) (95% CI)	15.7 (14.3-NR)	NR§ (NR-NR)	0.75	0.23
Best ORR (%) (95% CI)	50 (40.9–59.1)	55.5 (46.4–64.3)	−	0.88
Median duration of response (mo) (95% CI)	5.7 (4.9−7.2)	9.2 (6.8–10.4)	0.53	0.006
Median duration of disease control (mo) (95% CI)	4.9 (3.9−5.7)	7.8 (6.8−9.7)	0.52	<0.001

*m = median. §NR = not reached.

Conclusions: Overall, 1L Tx with cis–pem–bev followed by mtc bev or bev+pem is well-tolerated. Continuation mtc with bev+pem results in the most pronounced mPFS (10.2 mo) and reduction in risk of progression (50%, HR = 0.50) observed in this setting of patients with nsNSCLC who achieve disease control.