Presidential Session II

Sunday 25 September 2011, 12:20−14:40

7LBA LATE BREAKING ABSTRACT

A Multicentre Randomised Trial of Ibandronate Compared to Single Dose Radiotherapy for Localised Metastatic Bone Pain in Prostate Cancer (RIB)

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Background: Single dose radiotherapy (RT) is standard treatment for patients with localised metastatic bone pain. We compare Ibandronate (IB), a bisphosphonate drug, with RT for treating metastatic bone pain in prostate cancer patients.
Material and Methods: 470 patients were randomised to receive either a single dose of 8 Gy local RT or a single 6 mg intravenous infusion of IB. Patients reported their primary site of pain at baseline, then 4, 8, 12, 26 and 52 weeks after treatment. After reassessment at 4 weeks, non-responders crossed over to the alternative therapy, receiving their second treatment no later than week 8. The primary endpoint was pain relief at 4 and 12 weeks, compared to baseline. Pain relief was measured using a combination of analgesic use and pain score, based on two methods: (i) WHO pain ladder and (ii) analgesic use defined in morphine equivalents (Mercadante 1993), where a positive difference from baseline indicates worsening pain relief. The trial was powered (90%) to detect a difference in WHO response rate from 70% (RT) to 85% (IB).
Results: The median follow-up was 11.6 months. Baseline characteristics (age, site of pain, prior treatment, performance status) were well-balanced. The WHO response rate at 4 weeks was 53% (RT) vs 49% (IB), $p = 0.49$; and at 12 weeks 49% vs 56%, $p = 0.24$. Using the Mercadante score, the mean difference from baseline to 4 weeks was −3.2 units (RT) vs +1.2 (IB), $p = 0.11$; and to 12 weeks −0.2 vs −1.7, $p = 0.73$. However, the proportion of patients with a high score difference at 4 weeks ($\geqslant$+5.86 units) was 10% (RT) vs 20% (IB), $p = 0.004$. At 6 months the mean differences were +3.99 (RT) vs +1.95 (IB) $p = 0.66$. There was no difference at 12 months. The proportion crossing over treatments was 31% (IB) and 24% (RT), $p = 0.10$. The median survivals (months) were 11.8 (only RT), 11.4 (only IB), 12.7 (RT then IB), 16.8 (IB then RT).
Conclusions: When treating uncomplicated localised metastatic bone pain from prostate cancer this large trial generally shows no material difference between a single infusion of ibandronate and a single dose of RT. There appeared to be more patients in the IB group with worse Mercadante scores at 4 weeks (compared to baseline), consistent with more IB patients needing re-treatment after 4 weeks. Importantly, there was no long-term difference in pain relief between IB and RT at 6 or 12 months. Single doses of bisphosphonates could have an important role in the treatment of metastatic bone pain.

Presidential Session III

Monday 26 September 2011, 12:15−14:25

8LBA LATE BREAKING ABSTRACT

Delivering Affordable Cancer Care in High-income Countries: a *Lancet Oncology* Commission

R. Sullivan[1], J. Peppercorn[2], K. Sikora[3], J. Zalcberg[4], N. Meropol[5], E. Amir[6], D. Khayat[7], P. Boyle[8], I. Tannock[6], T. Fojo[9]. *[1]King's College London − King's Health Partners Integrated Cancer Centre, London, United Kingdom; [2]Duke Cancer Institute, Duke University Medicial Centre, Durham, USA; [3]CancerPartnersUK, Head Office, London, United Kingdom; [4]Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia; [5]University Hospitals Seidman Cancer Center Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, USA; [6]Division of Medical Oncology and Hematology, Princess Margaret Hospital and University of Toronto, Toronto, Canada; [7]Hôpital Pitié-Salpêtrière, Division of Oncology, Paris, France; [8]International Prevention Research Institute, Head Office, Lyon, France; [9]Medical Oncology Branch Center for Cancer Research, National Cancer Instutute, Bethesda, USA*

The burden of cancer is growing, and the disease is becoming a major unsustainable economic burden for all developed countries. In 2008, the worldwide cost of cancer due to premature death and disability (not including direct medical costs) was estimated to be US$895 billion. This is not simply due to an increase in absolute numbers, but also the rate of increase of expenditure on cancer. What are the drivers and solutions to the so-called cancer-cost curve in developed countries? How are we going to afford to deliver high quality and equitable care? Here, expert opinion from health-care professionals, policy makers, and cancer survivors has been gathered to address the barriers and solutions to delivering affordable cancer care. Although many of the drivers and themes are specific to a particular field − eg, the huge development costs for cancer medicines − there is strong concordance running through each contribution. Several drivers of cost, such as over-use, rapid expansion, and shortening life cycles of cancer technologies (such as medicines and imaging modalities), and the lack of suitable clinical research and integrated health economic studies, have converged with more defensive medical practice, a less informed and overly bureaucratic regulatory system, a lack of evidence-based sociopolitical debate, and a declining degree of fairness for all patients with cancer. Urgent solutions range from re-engineering of the macroeconomic basis of cancer costs (eg, value-based approaches to bend the cost curve and allow cost-saving technologies), greater education of policy makers, doctors, payers, and the general public, and an informed and transparent regulatory system. A radical shift in cancer policy is also required. Political toleration of unfairness in access to affordable cancer treatment is unacceptable. Equity in cancer care is a fundamental principle for all developed countries and access to effective health care is a human right. The cancer profession and industry should also take responsibility and not accept a substandard evidence base and an ethos of very small benefit at whatever cost; rather, we need delivery of fair prices and real value from new technologies. Delivering affordability also means educating the public that value-based care is not poor care; dramatically re-engineering care pathways to make them more cost effective; and introducing radical controls on the off-label use of cancer technologies.

Presidential Session III

Monday 26 September 2011, 12:15−14:25

9LBA LATE BREAKING ABSTRACT

Everolimus in Combination with Exemestane for Postmenopausal Women with Advanced Breast Cancer Who Are Refractory to Letrozole or Anastrozole: Results of the BOLERO-2 Phase III Trial

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Background: The mammalian target of rapamycin (mTOR) pathway is constitutively activated in hormone herapy-resistant advanced breast cancer (ABC). In phase II trials everolimus (EVE) showed promising efficacy both as monotherapy and in combination with endocrine therapy in patients with estrogen receptor positive (ER+) ABC. This double-blind, placebo-controlled phase III study (clinicaltrials.gov: NCT00863655; Trial Sponsor: Novartis Pharmaceuticals) evaluated EVE + exemestane (EXE) in patients with ER+ ABC refractory to letrozole or anastrozole.
Patients and Methods: Eligible patients were randomized (2:1) to EVE (10 mg/d) or matching placebo, with both arms receiving EXE (25 mg/d); treatment continued until progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) assessed by the investigators. Secondary endpoints included survival, response rate, and safety. A preplanned interim analysis was performed and reviewed by the independent data monitoring committee (IDMC) after observing 359 PFS events.
Results: 724 patients were randomized from 24 countries (485: EVE+EXE; 239: EXE). Baseline characteristics were well balanced; median age was 62 years; 56% had visceral involvement and 84% were sensitive to prior hormone therapy. Prior therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%) and chemotherapy (68%). At the interim analysis, the IDMC disclosed that the trial met its primary endpoint (PFS), as assessed by local investigators (HR: 0.43 [95% CI: 0.35–0.54], median 6.9 vs 2.8 months; $p = 1.4 \times 10^{-15}$), and that results were consistent across

the various subgroups. PFS analysis based on central assessment was also significant (HR: 0.36 [95% CI: 0.27–0.47], median 10.6 vs 4.1 months; $p = 3.3 \times 10^{-15}$). Both analyses crossed the pre-specified thresholds for significance. Response rates were 9.5% and 0.4% on EVE+EXE and EXE arms, respectively; $p < 0.0001$. Most common grade 3/4 adverse events were stomatitis (8% vs 1%), anemia (5% vs <1%), dyspnea (4% vs 1%), hyperglycemia (4% vs <1%), fatigue (3% vs 1%), and pneumonitis (3% vs 0%) for the EVE+EXE and EXE groups, respectively.
Conclusion: EVE, when added to an aromatase inhibitor, significantly improves PFS and response rate and has a manageable safety profile. EVE in combination with an aromatase inhibitor is a new therapeutic option for women with previously treated ABC.

Presidential Session III
Monday 26 September 2011, 12:15−14:25
10LBA LATE BREAKING ABSTRACT

The EORTC 10041/BIG 03−04 MINDACT (Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid ChemoTherapy) Trial: Patients' Baseline Characteristics and Logistics Aspects After a Successful Accrual

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Background: Personalized medicine and genomic risk profiling have been increasingly demanded for cancer management. The MINDACT trial investigates the added clinical value of the 70-gene profile (Mammaprint™) to standard clinicopathological criteria for the accurate selection of breast cancer (BC) pts for adjuvant chemotherapy (CT).
Material and Methods: All pts had their risk assessed by the 70-gene test [genomic (G) risk: high vs low] and by a modified version of Adjuvant! Online 8.0 [clinical (C) risk: high vs low]. G and C-high risk pts were proposed adjuvant CT. Discordant pts (G-low/C-high or G-high/C-low) were randomised between the two risk assessments to decide on adjuvant CT. Pts assigned to CT were offered a 2nd randomisation between an anthracycline-based regimen and the combination docetaxel–capecitabine. G-low and C-low risk pts were not assigned to CT. HR positive pts were offered an endocrine therapy randomisation (7 years of letrozole vs 2 years of tamoxifen followed by 5 years of letrozole) and ovarian function suppression if premenopausal.

	N (%)		
	G-high	G-low	**Total**
C-high	1827 (28)	1436 (22) CT: 718; no CT: 718	**3263 (50)***
C-low	678 (10) CT: 340; no CT: 338	2586 (40)	**3264 (50)***
Total	**2505 (38)**	**4022 (62)**	**6527**

*The 50−50 split is coincidental

Results: The trial was closed to screening in July 2011. Since March 2007, 11,300 pts were registered, 7,491 had the G test done, and 6,527 (58%) were enrolled in 104 sites in 9 countries. The proportion of registered/enrolled pts increased over time (46% in the 1st year to 63% in the last year). Monthly accrual increased from about 25 in the first year to over 200 pts in the last year. Current pts' baseline characteristics at enrolment are: 33% of pts <50 years of age, 80% were node negative, 71% had LN status verified by sentinel node biopsy, 83% had breast conservation surgery, 72% had tumors $\leqslant 2$ cm, 88% were HR positive (ER or PR+ or both), 11% HER2 positive, and 9% triple negative. Pts' risk allocations at enrolment are described in the table. As per status at enrollment the attribution to chemotherapy would be 11.6% lower using the 70-gene profile.
Conclusions: MINDACT is the largest European randomised prospective trial evaluating the clinical value of a gene expression profile for risk assessment and adjuvant CT prescription for BC. Accrual has been successfully completed and the trial's complex logistics, including real-time collection of frozen tumor tissue, were proven feasible in a multinational, multicentric setting.

Presidential Session IV
Tuesday 27 September 2011, 09:00−11:00
11LBA LATE BREAKING ABSTRACT

Identification of Novel Somatic Mutations in *SF3B1*, a Gene Encoding a Core Component of RNA Splicing Machinery, in Myelodysplasia with Ring Sideroblasts and Other Common Cancers

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Myelodysplastic syndromes (MDS) are a diverse group of chronic hematological malignancies, which, with the ageing population, have become the most prevalent myeloid cancer. Patients with MDS present with peripheral blood cytopenia, bone marrow dysplasia and an increased risk of transformation to acute myeloid leukemia (AML). The more recent WHO classification-based prognostic scoring system (WPSS) classifies MDS patients into five risk groups showing different survivals and probabilities of leukemic evolution. However, MDS patients demonstrate a high degree of morphological heterogeneity and variable clinical course irrespective of WHO subtype.
We reasoned that this heterogeneity may be attributable to distinct molecular lesions that contribute to MDS morphology and clinical outcome. We used massively parallel sequencing technology to identify somatically acquired point mutations across all protein-coding exons in the genome of 9 MDS patients.
We report the identification of novel somatically acquired mutations in patients with MDS. In 6/9 patients, we identified recurrent somatic mutations in a gene that encodes a core component of the RNA splicing machinery, *SF3B1*. To characterize the pevalence of *SF3B1* mutations, we undertook targeted resequencing of the gene in 2,087 samples from MDS patients, primary cancers and core cancer cell lines. Somatic mutations of *SF3B1* were found in 150/533 (28.1%) patients with MDS, 16/83 (19.3%) patients with MDS/MPN, and 2/38 (5.3%) patients with AML. The gene was also mutated in 1−5% of diverse other common tumor types including breast cancer, multiple myeloma and renal cancer. In patients with myeloid neoplasms, there were close relationships between mutant *SF3B1* and presence of ring sideroblasts ($P < 0.001$), and in multivariable analysis, *SF3B1* mutations were independently associated with better overall survival (HR = 0.18, $P = 0.028$) and lower risk of leukemic evolution (HR = 0.32, $P = 0.048$).
The close association between *SF3B1* mutation and ring sideroblasts across MDS is consistent with a causal relationship, and makes this the first gene to be strongly associated with a specific morphological feature in MDS. This molecular lesion has relevant clinical significance, as it is independently associated with a favorable clinical outcome.In conclusion, mutations in *SF3B1* implicate abnormalities of mRNA splicing, a pathway not previously known as a target for mutation, in the pathogenesis of MDS and cancer in general.