

Abiraterone acetate (AA), a selective androgen biosynthesis inhibitor, suppresses growth of CRPC through inhibition of persistent androgen synthesis from adrenal and intratumoral sources. In an international double-blind randomised trial of 1195 patients (pts), AA + prednisone (P) improved overall survival (HR = 0.646) in mCRPC progressing after docetaxel (D), compared with placebo + P. Here we retrospectively assess the effect of AA on patient-reported fatigue in this study.

Material and Methods: In this study of oral AA (1 g QD) + P (5 mg BID) vs placebo + P in mCRPC post-D, fatigue was assessed at baseline and each treatment cycle until discontinuation, using the Brief Fatigue Inventory (BFI) questionnaire. Fatigue intensity (worst fatigue item only) and fatigue interference (average of interference with general activity, mood, walking, work, relationships, enjoyment of life) were evaluated; scores were analysed post hoc for changes over time. All analyses were conducted using responder definitions (founded on distribution-based calculations) of clinically significant changes in eligible pts (i.e. with baseline score of ≥ 5 on BFI worst fatigue item/interference scale).

Results: 797 pts were randomised to AA and 398 to placebo. Median treatment duration was 8 and 4 months, respectively. Baseline BFI scores were not different between groups. AA yielded significantly better fatigue outcomes than placebo (Table). With AA, time to improvement in fatigue intensity was shorter and more pts showed improvement in fatigue intensity and interference. AA also delayed progression of fatigue intensity and interference. The fatigue profile of AA was superior to placebo from Cycles 1 to 15.

Conclusions: In post-D mCRPC, in addition to overall survival benefits, therapy with AA + P delays fatigue progression and produces clinically significant improvements in fatigue scores compared to baseline. Furthermore, AA improved fatigue more rapidly than placebo.

	AA N = 797	Placebo N = 398	p Value
BFI-Intensity			
Improvement, improved/eligible pts (%)	221/384 (58)	75/186 (40)	0.0001 ^a
Time to improvement [median], days	59	194	0.0114 ^b
Time to progression [25th percentile], days	232	139	0.0014 ^b
BFI-Interference			
Improvement, improved/eligible pts (%)	103/189 (55)	35/92 (38)	0.0096 ^a
Time to improvement [median], days	57	113	0.0809 ^b
Time to progression [25th percentile], days	281	139	0.0006 ^b

^a Chi-square test; ^b Log-rank test.

Poster Presentations (Sun, 25 Sep, 14:00–16:30) Genitourinary Malignancies – Prostate Cancer

7016

POSTER

Second Line Chemotherapy After Docetaxel Among Symptomatic Castration-Resistant Prostate Cancer (CPRC) Patients – GETUG-P02 Randomized Phase II Trial

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Background: Most patients (pts) relapse after first-line treatment with docetaxel. Trials with alternative agents were conducted among healthy pts (80% with OMS < 2, 80% < 70-year old, < 50% without pain). We designed a pragmatic second-line chemotherapy randomized phase II trial among symptomatic CRPC pts either old or with comorbidities.

Material and Methods: We assessed 3 routinely used drugs: mitoxantrone (MX: 12 mg/m²/3 wk), oral etoposide (VP: 25 mg bid/d1 to 14/3 wk), oral vinorelbine (VN: 60–80 mg/m²/d1 & d8/3 wk). The primary objective was objective palliative response defined by a decrease pain and/or analgesic consumption without disease progression. We prospectively assessed quality of life [QoL, (QLQ-C30, PR25)] and, for elderly, autonomy (ADL, IADL) and depression (GDS). The arms were stratified on progression-free interval from docetaxel and PSA doubling time.

Results: 92 pts were equally included in the 3 arms. 48 (52%) were more than 70-year old. Median time from docetaxel was 5.8 months. Pts and

disease initial characteristics were similar in each arm: 28% of pts had comorbidities, median baseline EVA for pain was 4, median concomitant treatments number was 3. Median cycles number was 3 in VP and 5 in MX and VN. Respectively 1, 3 and 1 pts withdrawn due to toxicities in MX, VP and VN arm. Grade 3–4 neutropenia occurred for 21% and 23% of MX and VN pts. Grade 3–4 anemia and asthenia were respectively observed for 16% and 13% of VP pts, and for 3% in MX and VN arms. Objective and global palliative response rates were respectively 17%, 22% (MX), 14%, 18% (VP) and 11%, 22% (VN). Corresponding median palliative response durations were 4.3, 4.9 and 2.1 months. Analgesic (partial+stable) response was respectively 92%, 93% and 77% in MX, VP and VN arm and corresponding median analgesic response duration were 10.6, 6.5 and 10.5 months. Median palliative PFS (OS) was respectively 3.4, 2.0 and 2.3 (10.6, 8.4, 12.6) months in MX, VP and VN arm. QoL did not decline over treatment for 89% of pts.

Initial autonomy loss and risk of depression (GDS ≥ 5) were respectively noted for 40% and 47% of elderly, with no relationship with palliative response. Response rate and duration were similar among > 70-year old pts. **Conclusions:** MX, VP and VN induced palliative response among pts either old or with comorbidities, with a good tolerance profile. However MX seems to be the best compromise in terms of response and profile of toxicities for this group of pts.

7017

POSTER

Establishing and Characterising New in Vitro Models of Docetaxel-resistance in Prostate Cancer

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Introduction: Docetaxel is first-line treatment for hormone-refractory prostate cancer (HRPC). A major limitation of this treatment is that, due to inherent or acquired drug resistance (RD), overall survival is increased by only 2.5 months on average. Here we established docetaxel-resistant prostate cancer cell line variants and characterised them as in vitro models of the clinical situation.

Materials and Methods: Using 22Rv1 (a cell line derived from a primary tumour) and DU145 (from a prostate cancer brain metastasis), we developed docetaxel-resistant variants, 22Rv1RD and DU145RD, respectively, through step-wise exposure to docetaxel over a 6 months period. Initial characterisation of these resistant variants, in comparison to their respective parallel-aged parent cells, included investigating their fold-resistance to docetaxel and their cross-resistance to other chemotherapeutic drugs. Changes in phenotypic characteristics were evaluated using proliferation assays; wound-heal migratory assays; soft agar assays; and invasion through ECM-coated transwells. Exosomes secreted by DU145 and DU145RD were isolated from their corresponding conditioned media, using a combination of filtration and ultracentrifugation. Western blotting was performed to evaluate the success of exosomes isolation and also for assessing cellular expression of the drug efflux pump, MDR1/P-gp.

Results: Docetaxel-conditioned variants were found to be substantially more resistant to docetaxel than their parallel-aged parent cell lines i.e. based on IC₅₀ values, 22Rv1RD and DU145RD are 71±8.4 and 107±7.4 fold resistant, respectively. Additionally, both resistant variants conferred cross-resistance to doxorubicin (8.3±1.2 for 22Rv1RD; 4.3±1.0 for DU145RD). While 22Rv1RD display low level cross-resistance to carboplatin (2.1±0.6) and 5-fluorouracil (1.6±0.2), DU145RD does not. DU145RD cells have increased motility (p < 0.05), migration (p < 0.01) and invasion (p < 0.05) capacity compared to DU145. Although 22Rv1RD cells were found to be somewhat less motile, migratory and invasive than 22Rv1, overall these cells are apparently not as aggressive as the DU145/DU145RD pair. Neither parent cell lines nor DU145RD express MDR-1/P-gp, whereas 22Rv1RD cells show low level expression; suggesting that this efflux pump may be in part, but not wholly, responsible for its drug resistance characteristics. Exosome isolation from DU145RD cells modulated the motility (p < 0.05) and invasive (p < 0.05) capacity of DU145 and invasiveness of 22Rv1 (p < 0.05).

Conclusion: New cell line models of docetaxel-resistance that may aid in the investigation of docetaxel-resistance and cross-resistance in prostate cancer have been developed. While MDR-1/P-gp may contribute to resistance and multi-drug resistance in 22Rv1RD, it does not seem to be involved in DU145RD resistance. Docetaxel-resistance in DU145RD is significantly associated with more aggressive cellular characteristics. Furthermore, exosomes released from DU145RD cell line and subsequently isolated from its CM can be taken up by secondary cells and affect the phenotype characteristics of such recipient cells.

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