Randomized phase II study of docetaxel with or without DMXAA (ASA404) in hormone-refractory metastatic prostate cancer (HRMPC)

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Background

- Vascular disrupting agents (VDAs) attack tumor blood vessels selectively, causing rapid shutdown of tumor blood flow[1–3]
- 5,6-dimethylxanthenone-4-acetic acid (DMXAA [ASA404, formerly AS1404]) is a small-molecule VDA with a unique mode of action[1]
- In animal models DMXAA shows additive or supra-additive anti-tumor effects with cytotoxics, including taxanes[4]
- DMXAA is being evaluated in clinical trials in combination with taxane or taxane plus platinum regimens in lung, prostate and ovarian cancers
- A randomized phase II study in non-small cell lung cancer reported a substantial survival benefit when DMXAA was added to paclitaxel-based chemotherapy (median survival of 14.0 months with DMXAA plus carboplatin and paclitaxel versus 8.8 months with carboplatin and paclitaxel alone)[5]

Objectives

- To compare the efficacy of DMXAA in combination with docetaxel with that of docetaxel alone in patients with progressive, hormone-refractory metastatic prostate cancer, previously untreated with chemotherapy
- To assess the safety and tolerability of DMXAA in combination with docetaxel
- To assess the effects of DMXAA on docetaxel pharmacokinetics (data not yet available)

Methods

Study design

- Randomized, multicenter, open-label, phase II study comparing patients receiving DMXAA plus docetaxel ('DMXAA arm') with patients receiving docetaxel alone ('standard therapy arm')
- Patients aged ≥18 yrs with histopathologically confirmed adenocarcinoma of the prostate
- Patients had metastatic, progressive, androgen-independent disease with no prior chemotherapy
- Progressive disease (with ongoing hormone ablation) was defined as at least one of the following:
  - Progressive disease according to RECIST criteria within last 30 days
  - One or more new lesions on bone scan within last 30 days with PSA (prostate-specific antigen) level of at least 5 ng/ml
  - Non-progressive (RECIST) disease or non-progressive bone scan with rising PSA from a baseline PSA > 5 ng/ml
- The first cohort of 6 patients in the DMXAA arm received therapy under early stopping rules for safety monitoring
- Treatment was given every 21 days for up to 10 cycles
- On day 1 of each 21-day treatment cycle, patients received:
  - Docetaxel as a 1-hour infusion (75 mg/m^2), then
  - DMXAA as a 20-minute infusion (1200 mg/m^2), if allocated
- Patients in the standard therapy arm who showed disease progression during treatment then had an option to receive up to 6 cycles of DMXAA monotherapy, administered weekly
- The dose of docetaxel could be modified for patients who experienced treatment-related toxicity
- Follow-up:
  - Imaging assessment 6-weekly until disease progression
  - PSA assessment 6-weekly until disease progression
  - Ongoing 3-monthly follow up

Study variables

- Primary safety outcomes: adverse events, laboratory abnormalities, effect on QTc interval and ophthalmic toxicity
- Efficacy endpoints: objective response rates, time to progression, duration of response and stable disease, PSA response rate (as per Bubley[6]) and time to PSA progression, median and 1-year survival

Results

Patient characteristics

- 74 patients were randomized (DMXAA arm, n = 35; standard therapy arm, n = 39)
- 2 patients in the DMXAA arm and 1 patient in the standard therapy arm were not treated (safety population: DMXAA arm, n=33; standard therapy arm, n=38)
- One patient in the DMXAA arm was not included in the eligible population due to major violation of protocol (eligible population: DMXAA arm, n=32; standard therapy arm, n=38)
- The two arms were well balanced for pre-treatment characteristics (Table 1)
- 4 patients switched from the standard therapy arm to receive DMXAA monotherapy after showing disease progression

Table 1: Baseline characteristics for eligible population

	DMXAA arm (n = 32)	Standard therapy arm (n = 38)
Median PSA (range) ng/ml	68.4 (9–3574)	82.2 (1–570)
Mean age (years)	68.8	66.5
ECOG performance status		
0	12 (37.5%)	16 (42.1%)
1	20 (62.5%)	19 (50.0%)
2	0	3 (7.9%)

Safety

- The number of patients who experienced one or more serious adverse events was similar in the DMXAA and standard therapy arms (14 and 13 patients, respectively)
- There were more cardiac SAEs (4) in the DMXAA arm than in the standard therapy arm (1). However, there was no consistent qualitative pattern to these and none was clearly attributable to treatment with DMXAA

Table 2: Serious adverse events by number of patients

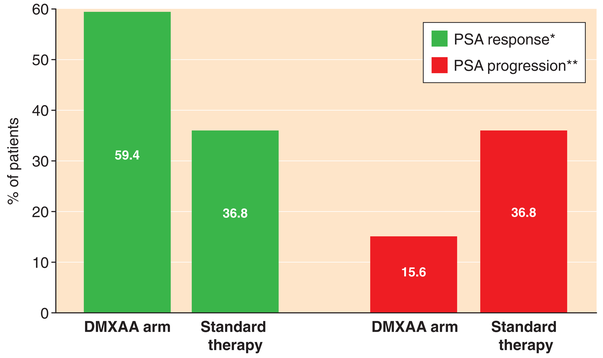
System organ class	DMXAA arm (n = 33)	Standard therapy arm (n = 38)
Blood and lymphatic system	4 (12%)	3 (8%)
Cardiac	4 (12%)	1 (3%)
Gastrointestinal	2 (6%)	3 (8%)
General and administration site	1 (3%)	1 (3%)
Immune system	1 (3%)	0
Infections and infestations	2 (6%)	4 (11%)
Injury and procedural complications	0	1 (3%)
Metabolic and nutrition	0	1 (3%)
Musculoskeletal and connective tissue	1 (3%)	3 (8%)
Neoplasm progression	0	1 (3%)
Nervous system	1 (3%)	3 (8%)
Renal and urinary	0	3 (8%)
Vascular	1 (3%)	1 (3%)

Efficacy – PSA response

- PSA response data are available from 70 eligible patients, as shown in Figure 1
- PSA response rate was 59% in the DMXAA arm vs 37% in the standard therapy arm
- PSA progression rate was 16% in the DMXAA arm vs 37% in the standard therapy arm

Figure 1: PSA response

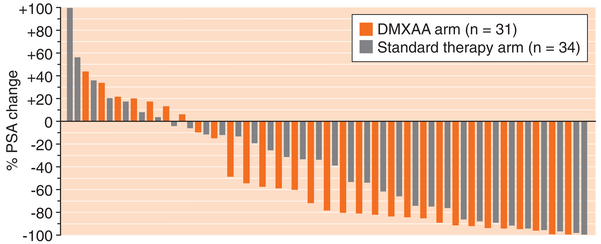
(n= 32 for DMXAA arm, n= 38 for standard therapy arm)



*Confirmed 50% or greater decrease in PSA vs baseline,
**Confirmed 25% or greater increase in PSA vs nadir or baseline (whichever is lower)

- Figure 2 shows the maximum fall in PSA for each patient (n=65, as 1 patient in the DMXAA arm and 4 patients in the standard therapy arm had no post-baseline PSA values)
- Patients in the DMXAA arm experienced greater median reduction in PSA than those in the standard therapy arm (79% vs 36% for the whole groups and 83% vs 62% for the subgroups of patients showing any PSA fall)
- The median time to PSA nadir for patients showing a PSA fall from baseline was 96 days in the DMXAA arm compared with 120 days in the standard therapy arm

Figure 2: Maximum percentage reduction in PSA for each individual patient



Conclusions and discussion

- Addition of DMXAA to standard doses of docetaxel was well tolerated
- The PSA response rate was markedly higher in patients receiving DMXAA plus docetaxel than in those receiving docetaxel alone
- Treatment with DMXAA plus docetaxel was associated with larger and more rapid reductions in PSA levels than treatment with docetaxel alone
- These data suggest that, when used in combination with docetaxel, DMXAA has activity in HRMPC
- These findings are consistent with positive response rate and survival data in non-small cell lung cancer and response findings in ovarian cancer. Taken together, these data suggest that, when used in combination with chemotherapy, DMXAA has potential in a variety of solid tumors[5,7]

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ASCO Chicago 2007