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Chemotherapy at First Diagnosis of Advanced Prostate Cancer - Revolution or Evolution? Findings from a British Uro-oncology Group UK Survey to evaluate oncologists' views on first line docetaxel in combination with androgen deprivation therapy in castrate sensitive metastatic and high risk / locally advanced prostate cancer

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INTRODUCTION

The year 2004 was a turning point for the management of advanced or metastatic prostate cancer with the reporting of two positive phase III trials of docetaxel (1, 2). Until then, treatment had been limited to androgen deprivation therapy (ADT) with the aims of symptom palliation and delaying disease progression. Cytotoxic chemotherapy with mitoxantrone and prednisolone (2) had demonstrated modest analgesic benefits, but no impact on overall survival (OS). TAX 327 (1), alongside the SWOG 99-16 trial (2), marked the genesis of a new era for the uro-oncology community, providing hope on the horizon for patients with advanced prostate cancer. The TAX 327 trial demonstrated that docetaxel, with concomitant prednisolone, improved median overall survival in men with metastatic Castration-Resistant Prostate Cancer (mCRPC) compared to mitoxantrone plus prednisolone (19.2 months v 16.3 months respectively; HR=0.79; p=0.0004) (3). Now, a decade on, we see a proliferation of management options for mCRPC and the sequencing of these treatments is the subject of ongoing debate amongst oncologists and urologists (4-9).

There is now increasing focus on earlier disease at the point where metastatic prostate cancer is not yet resistant to castration therapy. These patients are often fitter than those with CRPC, and may be better able to tolerate systemic therapy. Further, if the hazard ratios for OS can be translated from the CRPC to the castrate sensitive prostate cancer (CSPC) setting, then by virtue of being earlier in the patient's lifespan they may make a greater contribution to improving OS. The addition of docetaxel to first-line ADT for men with metastatic CSPC has been the key question of three recently reported trials: GETUG-AFU-15 (10); E3805 CHARTED (11) and STAMPEDE (12).

The GETUG-AFU-15 study (10) randomised 385 men in a 1:1 ratio to receive continuous ADT alone or in combination with docetaxel (75 mg/m²) every 3 weeks for up to 9 cycles. After a median follow-up of 50 months, there was no difference in OS: median 58.9 months in the ADT plus docetaxel group and 54.2 months for ADT alone group (HR = 1.01, 0.75-1.36). A significant benefit was detected for docetaxel in the following secondary endpoints: median biochemical progression free survival (22.9 v 12.9 months; HR= 0.72 (0.57-0.91); p=0.005); clinical progression free survival (23.5 v 15.4 months; HR= 0.75 (0.59-0.94); p=0.015). However, with no benefit in the primary endpoint of OS, the group concluded that docetaxel should not be used as part of first-line treatment for patients with non-castrate-resistant metastatic prostate cancer. The GETUG study also reported a

21% incidence of febrile neutropenia. There were 4 treatment related deaths in the chemotherapy group, two of which were neutropenia related. Following this, the data monitoring committee recommended the use of granulocyte colony-stimulating factor after which there were no further treatment-related deaths.

The E3805 CHAARTED trial (11) randomised 790 men equally to ADT alone versus ADT + docetaxel (75mg/m² every 3 weeks for 6 cycles; no prednisolone). Men started docetaxel within 4 months of the initiation of ADT and were stratified into high volume (HV) vs. low volume (LV) disease subgroups. High volume disease was defined as visceral metastases and/or 4 or more bone metastases with at least one beyond the pelvis and vertebral column. 72.8% of men in both arms had received no prior local treatment for prostate cancer. Of those who had relapsed with metastatic disease following initial radical management, 4.5% of patients in the combined arm and 4.1% of patients in the ADT alone arm had been exposed to adjuvant hormone therapy. The study demonstrated a significant OS advantage for the docetaxel and ADT combination: median OS of 57.6 months v 44.0 months (HR=0.61 (0.47-0.80); p<0.001). The results from subgroup analyses showed an even greater benefit for men with HV disease with a 17 month improvement in median OS (49.2 months v 32.2 months; HR=0.60 (0.45-0.81); p<0.001). There was no significant difference in OS for the LV group (HR=0.60 (0.32-1.13); p=0.11) and the authors concluded that longer follow up will be required to determine whether a clinically significant benefit exists. Use of granulocyte colony-stimulating factor in CHAARTED was at the investigator's discretion and the incidence of neutropenic fever in was 6% with one treatment related death.

The GETUG group recently presented a retrospective re-analysis of their study according to the disease volume definitions used in CHAARTED, and with a longer median follow up of 82.9 months. The patient distribution between HV and LV differed to CHAARTED with HV patients accounting for 47.5% of men in the GETUG study compared to 65% of men in CHAARTED. In GETUG, the number of men in the ADT-alone arm who subsequently received docetaxel on progression was higher at 80% compared to 34% in CHAARTED. Again there was no significant difference observed in OS, even on sub-group analysis based on disease volume. However, a non-significant 4 month increase in OS was seen in the underpowered HV group (39 months verses 35.1 months: HR=0.8 (0.6-1.2) p=0.35). Combining ADT and docetaxel again showed a significant benefit in terms of bPFS and cPFS (13).

STAMPEDE is a novel study with a multi-arm, multi-stage (MAMS) design which has investigated a number of treatment strategies including the addition of docetaxel to ADT and compared this to standard of care (ADT alone). STAMPEDE included men with metastatic or node positive prostate cancer in addition to those with high risk locally advanced disease (defined as 2 or more of the following risk factors: T3/T4 or PSA≥40ng/ml or Gleason Score 8 -10) (12). Men who had relapsed after previous radiotherapy or prostatectomy were eligible if they had one or more of the following progression factors: PSA≥ 4ng/ml and a PSA doubling time of less than 6 months, PSA ≥20ng/ml, positive nodal disease or metastases. This study did not sub categorise high volume and low volume metastases. The assessment of ADT +/- docetaxel (75mg/m² every 3 weeks for 6 cycles; prednisolone 10mg daily) took place between 2005 and 2013; with 1184 men randomised to ADT alone, and 592 to ADT and docetaxel.

Results presented at the ASCO meeting 2015 showed that at a median follow up of 42 months there was a significant improvement in OS for the group receiving docetaxel and ADT in combination: median OS of 77 months v 67.0 months (HR=0.76 (0.63-0.91) p=0.003). This difference was even greater for men with metastatic disease with a reported 22 month increase in median OS from 43 months to 65 months (HR= 0.73 (0.59-0.89) p=0.02). For men with non-metastatic disease, there were only 93 OS events at the data cut so it was too early to determine significance. There were

also significant benefits seen in terms of Failure Free Survival (FFS), defined as the first of the following events: PSA failure, local failure, lymph node failure, distant metastases or prostate cancer death. The results for the entire group reported a median FFS of 21 months for the ADT arm and 37 months for the ADT and docetaxel group (HR=0.62 (0.54-0.70) $p < 0.000000001$). For the non-metastatic group, the FFS benefit had a significant HR of 0.57 (0.42 – 0.76). The toxicity was higher for the docetaxel combination with 51% Grade 3+ events compared to 31% for ADT alone and a 12% rate of febrile neutropenia. The STAMPEDE results demonstrated that docetaxel improved OS for CSPC and the conclusion was that this should be considered standard of care for suitable men with newly diagnosed metastatic prostate cancer. Publication of this STAMPEDE data in a peer reviewed journal is awaited.

Up front chemotherapy combined with ADT may effectively treat hormone-resistant cells at diagnosis, potentially achieving a prolonged initial response. First line combination chemotherapy with ADT would result in more men receiving chemotherapy earlier in their disease course, when potentially fitter and better able to tolerate treatment. However, some men at low risk of death from prostate cancer may never require chemotherapy and may be unnecessarily exposed to the toxicity of this treatment.

This original paper presents data from a survey of members of the British Uro-oncology Group (BUG) which assessed whether uro-oncologists' practice has changed or may be likely to change in the future in various clinical settings based on the findings reported from GETUG-AFU-15, E3805 CHAARTED and STAMPEDE.

MATERIALS AND METHODS

BUG issued a semi-structured online questionnaire, comprising 21 questions, to its membership of specialist urological oncologists (see Appendix 1). The survey was written by the authors to reflect the data from the recent studies. The majority of questions were multiple-choice, allowing the respondent one answer. For questions asking oncologists for factors influencing their decisions, a free text box was provided. The questionnaire was sent via e-mail link to 160 uro-oncologists practising across the UK. The initial invitation to participate was sent two weeks following oral presentation of the STAMPEDE data at the ASCO annual meeting, June 2015. Links to the abstracts of GETUG-AFU-15, E3805 CHAARTED and STAMPEDE were attached with the survey for respondents to review prior to completing the survey. The questionnaire link remained open until 30 September 2015, following which the responses were analysed.

RESULTS

Participants

One hundred and eleven participants completed the survey, all confirming that they treat prostate cancer. Across the country, there was a wide range in the volume of new cases of metastatic prostate cancer discussed annually in local MDT meetings, as shown in figure 1a. In these MDTs, most individual oncologists see between 50 and 100 new patients each year (figure 1b).

Patient population

Of the new cases of metastatic prostate cancer discussed at local MDT each year, most oncologists believe that that over 25% have high volume disease (by the CHARTED criteria) (figure 1c). Eighty-nine per cent of oncologists felt between 26-76% of their patients would be considered medically fit to receive docetaxel chemotherapy (regardless of whether or not they may be willing to receive chemotherapy) (figure 1d).

Influence of CHARTED / STAMPEDE on clinical practice

A third of the participants said that the CHARTED study had influenced their clinical practice during the past 12 months (Figure 2a) while 87% stated that STAMPEDE will influence their clinical practice in the future (Figure 2b).

When asked how many patients with metastatic prostate cancer the clinicians had treated with docetaxel in combination with ADT as first line therapy in the past 12 months, 47% of oncologists answered none, whereas 47% had treated 1-10 patients, and 5% had treated more than 10 patients (Figure 2c).

Participants were asked to consider whether, if funded, they would offer docetaxel in combination with ADT as first line therapy for hormone sensitive disease in the future. Four different clinical scenarios were given, based on the data reported from the CHARTED and STAMPEDE studies.

When asked if they would offer the combination treatment to men with high volume metastatic prostate cancer 96% of the participants replied “Yes”, with 4% answering “possibly” (figure 3a). Additionally 54% of respondents stated that they anticipated delivering this treatment to over 50% of men presenting with HV metastatic disease (figure 3b).

However, only 46% of clinicians stated that they would offer the docetaxel/ADT combination as a first line therapy to men with low volume metastatic prostate cancer, another 46% stating that they would “possibly” offer this regimen (figure 3c). The proportion of men with LV metastatic disease that respondents anticipated treating with the combination was also lower with only 22% anticipating treating over 50% of men (figure 3d).

The third scenario concerned men with non-metastatic locally advanced prostate cancer (defined as node positive or at least 2 of: T3/4; PSA \geq 40; Gleason \geq 8). Only 14% of oncologists replied that they would offer the docetaxel combination treatment as first-line therapy, although 54% stated it was a possibility, 12% did not know and 19% of respondents would not offer this treatment (figure 3e).

Of those respondents who would treat men with non-metastatic disease, the proportions of such men they anticipated delivering docetaxel chemotherapy to are shown in figure 3f.

Finally, regarding treatment with docetaxel in combination with ADT as first line therapy for men with metastatic progression who have previously received radical treatment (Prostatectomy or Radiotherapy). Forty-six percent of the respondents would use this regimen, and 39% would “possibly” use it (figure 3g). When asked what proportion of these men they anticipate treating with the first line combination 33% stated up to 25% of patients, 31% stated between 25 and 50% of patients, and 15% stated between 50 and 75% of patients (Figure 3h).

The Oncologists were also asked to estimate how many additional patients they will treat with first line ADT and docetaxel over the next 12 months, 51% of clinicians expect to treat up to 25 additional patients, 20% expect to treat 26-50 patients, and 19% predict the number of patients to be over 50 (Figure 4).

Factors influencing clinical decisions

The survey included 4 questions regarding key factors that influenced the uro-oncologists' decisions to treat with up front docetaxel in the 4 differing clinical settings.

In the de-novo metastatic settings, reported factors included patient fitness, performance status, comorbidities, age, life expectancy, disease volume / burden (especially visceral metastases), Gleason score, PSA level, the presence of up to date to guidelines, and patient preference.

In both the non-metastatic setting and in the metastatic progression post radical treatment setting, factors included funding, patient fitness, performance status, comorbidities, age, bulk of nodal disease, histological risk factors / Gleason score, PSA level, STAMPEDE overall survival data and patient preference.

DISCUSSION

This survey reports oncologists' attitudes towards a major change in practice in the standard of care for men with newly diagnosed advanced prostate cancer in the UK. Following the oral and abstract presentations of the STAMPEDE chemotherapy data, 96% of oncologists indicated that they would offer docetaxel in combination with ADT as a first line therapy option to suitable men with high volume metastatic prostate cancer. A significant proportion of these patients are considered fit for this treatment. However, only 46% of respondents would also offer this therapy to men with low volume metastatic disease. This response would seem likely to reflect the sub-group analysis of OS in low volume disease in the CHAARTED study which did not show a statistically significant difference. However, as a counter argument, the hazard ratio in this subgroup is similar in CHAARTED to the HV subgroup. Furthermore, the data are likely to be immature simply because LV patients were added into the CHAARTED trial as a protocol amendment during its recruitment and will inevitably experience events at a later point. STAMPEDE, which showed a survival advantage in its M1 subgroup as a whole has not presented data on a HV/LV split (and was not set up to do so). However this distinction seems to remain as a decision making factor in many oncologists minds.

There is more uncertainty as to whether combined docetaxel and ADT as first line therapy for men with non-metastatic disease will be adopted into practice in the UK despite an advantage in FFS. This caution may stem from the absence of an overall survival benefit for chemotherapy in men with non-metastatic but locally advanced or high risk localised disease. The use of chemotherapy in the adjuvant setting following radiotherapy has been investigated in RTOG 0521 which randomised men with high risk prostate cancer to ADT plus radical radiotherapy or ADT plus radical radiotherapy plus 6 cycles of adjuvant docetaxel at 75 mg/m² with prednisolone commencing 4 weeks following the completion of radiotherapy. Results were reported at ASCO General Meeting 2015 (13). Four year OS rates were 89% [95% CI: 84-92%] in the ADT plus radiotherapy arm and 93% [95% CI: 90-96%] in the ADT plus radiotherapy plus docetaxel arm (1-sided p = 0.03, HR = 0.68 0.44-1.03). Prostate cancer specific mortality was better than expected in the design of the study and longer follow-up is required to clearly understand the benefit docetaxel adds in this population.

Various factors influenced uro-oncologists' decision to offer first line chemotherapy in combination with ADT. Key themes were patient related factors including co-morbidities, performance status and patient preference, and disease related factors such as Gleason grade, PSA and bulk of metastatic disease. As well as evidence presented from GETUG-15; CHAARTED and STAMPEDE, British uro-

oncologists also need to consider UK funding issues when offering new management strategies. This is not just for docetaxel itself, but they also need to address the increase workload associated with additional men receiving early chemotherapy which will have implications on the workload of oncologists and that of chemotherapy units.

Nationally, discussions are taking place on how units can best expand services with resource limitations to implement this change in clinical practice. In the survey, respondents proposed a need for updated national guidelines which may facilitate this.

Findings from the survey indicate the results from the three studies (GETUG-15; CHARTED and STAMPEDE) will have an impact on the future management of patients with metastatic prostate cancer. The survey highlighted the complexities surrounding the clinical implementation of the data from these studies, including changes in referral pathways with the early involvement of oncologists in such patients' care, increases in workloads for oncologists and chemotherapy units and the need for national approval for re-imburement of these treatments. The uro-oncology community is engaged with emerging evidence to attain access for early chemotherapy for all suitable patients across the UK. Oncologists and urologists, together with the whole MDT, need to work within the boundaries of reimbursement and access regulations, individualising treatment for patients' needs.

CONCLUSION

We have witnessed a 'revolution' with powerful new data redefining standard of care. The evolution in the management of advanced prostate cancer continues. Without doubt, 2014-2015 represents another significant turning point in improving the management of patients with advanced prostate cancer. BUG aims to continue to share best practice and thanks its membership for contributing to this project.

Conflict of Interest

Dr R Davda reports non-financial support from Janssen, non-financial support from Ipsen, non-financial support from Takeda, grants and non-financial support from Astellas, outside the submitted work.

Dr S Hughes reports personal fees and non-financial support from Astellas, personal fees and non-financial support from Janssen, personal fees from Sanofi, personal fees from Pierre Fabre, outside the submitted work.

Dr R Jones reports grants from Pfizer, grants from Novartis, during the conduct of the study; grants and personal fees from Pfizer, grants, personal fees and non-financial support from Novartis, grants, personal fees and non-financial support from GSK, outside the submitted work.

Dr S Crabb reports personal fees from Sanofi, personal fees from Astellas, personal fees from Bayer, grants from AstraZeneca, personal fees from Janssen, outside the submitted work.

Mrs J Troup has nothing to disclose.

Prof H Payne reports personal fees from Sanofi Aventis, personal fees from Janssen, grants from Astellas, personal fees from AstraZeneca, personal fees from Sandoz, personal fees from Takeda, personal fees from Amgen, personal fees from Ipsen, personal fees from Ferring, outside the submitted work.

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Appendix 1: online survey questions

BUG Survey: Chemotherapy and Androgen Deprivation Therapy (ADT) for Advanced Prostate Cancer

There have been recent developments in the management of metastatic (advanced) prostate cancer. The abstracts from three studies investigating the use of initial chemotherapy are detailed below if you wish to copy and paste to open in your web browser. Two of these trials have now demonstrated a survival advantage when docetaxel is given in combination with androgen deprivation therapy (ADT) for first line therapy.

On behalf of the British Uro-oncology Group (BUG), we would be grateful if you would answer the questions in this survey. Your answers will be anonymous, but the pooled results will hopefully help us to try and determine whether these three studies have already influenced, or are likely to influence, future uro-oncology practice in the UK.

* Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial.
<http://www.ncbi.nlm.nih.gov/m/pubmed/23306100/>

* CHARTED: ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer
http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/LBA2?sid=c963c9ed-cf5b-4a5f-b1bd-f6adf75e0f80

* Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First overall survival results from STAMPEDE
http://abstracts.asco.org/156/AbstView_156_147721.html

1. Do you treat prostate cancer?

- Yes
- No

2. Approximately how many new cases of metastatic prostate cancer are discussed at your MDT in a year?

- 1-50
- 51-100
- 101-200
- 200-300
- >300

3. Approximately what proportion of the cases referred to in Question 2 have HIGH volume disease (defined as visceral metastases and/or more than 4 bone metastases at least one of which is outside the pelvis or spine)?

- <15%
- 15 – 25%

- 26 – 35%
- 36 – 50%
- 51 – 75%
- >75%

4. Approximately what proportion of the cases referred to in Question 2 would you consider medically fit to receive docetaxel (regardless of whether or not they may be willing)?

- <25%
- 26 – 50%
- 51 – 75%
- >75%

5. Approximately how many men with metastatic prostate cancer are referred to your personal practice in a year?

- 1-25
- 51-100
- 101-200
- >200

6. Has the CHARTED data influenced your clinical practice in the last 12 months?

- Yes
- No
- Possibly
- Don't Know

7. Within your personal practice, how many patients with metastatic prostate cancer have you treated with docetaxel in combination with ADT as first line therapy in the past 12 months?

- None
- 1-10
- 11-20
- 21-50
- >50

List any factors that have influenced your answer to Question 7:.....

8. Will the STAMPEDE docetaxel data influence your clinical practice in the future?

- Yes
- No
- Possibly
- Don't know

9. If funded, would you offer docetaxel in combination with ADT as a first line therapy option to men with HIGH volume metastatic prostate cancer in the future? (defined as visceral metastases and/or 4 or more bone metastases with at least 1 beyond pelvis and vertebral column)

- Yes
- No
- Possibly
- Don't know

10. In your personal practice, what proportion of men with HIGH volume metastatic prostate cancer do you anticipate that you will treat with first line combination ADT and docetaxel in the future?

- None
- 1-25%
- 26-50%
- 51-75%
- 76-100%
- Don't know

11. In this setting:

Please list any factors that could influence your decision to treat with first line chemotherapy in combination with ADT

Please list any factors that could influence your decision NOT to treat with first line chemotherapy in combination with ADT

12. If funded, would you offer docetaxel in combination with ADT as a first line therapy option to men with LOW volume metastatic prostate cancer in the future?

- Yes
- No
- Possibly
- Don't know

13. In your personal practice, what proportion of men with LOW volume metastatic prostate cancer do you anticipate that you will treat with first line combination ADT and docetaxel in the future?

None

- 1-25%
- 26-50%
- 51-75%
- 76-100%
- Don't know

14. In this setting:

Please list any factors that could influence your decision to treat with first line chemotherapy in combination with ADT

Please list any factors that could influence your decision NOT to treat with first line chemotherapy in combination with ADT

15. If funded would you offer docetaxel in combination with ADT as first line therapy for men with nonmetastatic locally advanced prostate cancer in the future (defined as node positive or at least 2 of: T3/4 or PSA \geq 40 or Gleason \geq 8)?

- Yes
- No
- Possibly
- Don't know

16. In your personal practice, what proportion of men with non-metastatic locally advanced prostate cancer do you anticipate that you will treat with first line combination ADT and docetaxel in the future?

- None
- 1-10%
- 11-25%

- 26-50%
- 51-75%
- 76-100%
- Don't Know

17. In this setting:

Please list any factors that could influence your decision to treat with first line chemotherapy in combination with ADT

Please list any factors that could influence your decision NOT to treat with first line chemotherapy in combination with ADT

18. If funded, would you offer docetaxel in combination with ADT as first line therapy for metastatic progression to men who have previously been treated with radical prostatectomy (RP) or radical radiotherapy (RT)?

- Yes
- No
- Possibly
- Don't know

19. In your personal practice, what proportion of men who progress to develop metastatic prostate cancer, after primary therapy with RP or RT, do you anticipate that you will treat with first line combination ADT and docetaxel in the future?

- None
- 1-25%
- 26-50%
- 51-75%
- 76-100%
- Don't Know

20. In this setting:

Please list any factors that could influence your decision to treat with first line chemotherapy in combination with ADT for metastatic progression

Please list any factors that could influence your decision NOT to treat with first line chemotherapy in combination with ADT for metastatic progression

21. How many additional patients do you anticipate that you will treat with first line ADT and docetaxel in the next 12 months?

- None
- 1-10
- 11-25
- 26-50
- >50
- Don't know