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A phase III trial of docetaxel–estramustine in high-risk localised prostate cancer: A planned analysis of response, toxicity and quality of life in the GETUG 12 trial ☆

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ABSTRACT

Aim: To assess docetaxel–estramustine in patients with localised high-risk prostate cancer.
Patients and methods: After staging pelvic lymph node dissection, patients with high-risk prostate cancer randomly received androgen deprivation therapy (ADT) (3 years) + DE (4 cycles of docetaxel 70 mg/m^2/3 weeks + estramustine 10 mg/kg/d d1–5) or ADT alone. Local therapy was administered at 3 months.
Results: Four hundred and thirteen patients were accrued: T3–T4 (67%), Gleason score $\geqslant$8 (42%), PSA >20 ng/mL (59%), pN+ (29%). In the chemotherapy arm, 94% of patients received the planned four cycles of docetaxel. Local treatment consisted of radiotherapy in 358 patients (87%) (median dose 74 Gy in both arms). ADT was given for 36 months in both arms. A PSA response (PSA $\leqslant$0.2 ng/mL after 3 months of treatment) was obtained in 34% and 15% in the ADT + DE arm and in the ADT arm, respectively ($p < 0.0001$). Febrile neutropenia occurred in only 2%. Moderate to severe hot flashes occurred less often in the ADT + DE arm (2% versus 22%; $p < 0.001$). There was no toxicity-related death, no secondary leukaemia, and no excess second cancers. Chemotherapy had a negative impact on quality of life (global health status, $p = 0.01$; fatigue, $p = 0.003$; role functioning, $p = 0.003$; social functioning, $p = 0.006$) at 3 months but this effect disappeared at 1 year.
Conclusion: Docetaxel–estramustine can be combined safely with standard therapy in high-risk prostate cancer, with a promising PSA response rate and no negative impact on quality of life after 1 year. Long-term follow-up is required to assess the impact on relapse and survival.

1. Introduction

Prostate cancer is the most frequent cancer in most Western countries.[1,2] Although prostate cancer-related death is almost systematically due to metastatic dissemination, most patients who are diagnosed with prostate cancer nowadays have localised disease at presentation. Prognostic classifications are mostly based on local extension, the Gleason score and serum prostate-specific antigen (PSA). The nodal (pN) status, when available, was also shown to be an important prognostic parameter.[3] Although a variety of prognostic systems have been proposed, the specific definition used seems to have a minimal impact on prediction.[4] Classically up to 30–50% of patients in the high-risk group ultimately die of their cancer.[5,6]

There is now strong evidence that combining androgen deprivation therapy (ADT) with radiotherapy improves survival of patients with high-risk localised prostate cancer, compared to radiotherapy alone.[6–11] More recently, the ADT-radiotherapy combination was shown to be superior to ADT alone,[12] and a 3-year duration of ADT was shown to be superior to a 6-month duration.[13] In contrast, the role of pelvic radiotherapy continues to fuel debate.[14–16] Although prolonged ADT is usually recommended in patients with pN+ disease[17,18], it has not been fully established whether these patients should be managed with local treatment. The role of prostatectomy has not been randomly assessed, although this treatment is regarded by some authors as an option in patients with high-risk features.[19]

In other epithelial neoplasms, chemotherapeutic agents proven active in the metastatic setting yielded a higher survival benefit when used in the localised setting. In prostate cancer such a strategy has been hampered due to the lack of active chemotherapy. During the early 2000s however, docetaxel demonstrated anticancer activity[20,21] and survival improvement.[22,23] An increased response rate was suggested with docetaxel–estramustine, and a meta-analysis showed enhanced survival with chemotherapy plus estramustine versus chemotherapy alone.[24] This prompted the French Groupe d'Etude des Tumeurs Uro-Génitales (GETUG) to assess whether including docetaxel–estramustine in the treatment of patients with high-risk prostate cancer could improve outcome. This report focuses on the design, the treatments actually delivered, tolerance and quality of life observed in GETUG 12.

2. Patients and methods

2.1. Patient population

Men selected had high-risk prostate cancer with no detectable metastases. Eligibility criteria were as follows: histologically-proven adenocarcinoma of the prostate with at least one of the following high-risk features:

- Gleason score $\geqslant$8.
- A T3 or T4 stage according to the TNM classification.
- Serum PSA >20 ng/mL.
- Histologically-proven pelvic lymph node involvement.

Patients were required to have no evidence of metastases on bone scan and abdomino-pelvic computed tomography

scan (or magnetic resonance imaging) within the past 6 months (obtaining these imaging procedures within 6 weeks before accrual was recommended). A staging pelvic lymph node dissection (performed via a laparoscopic or an open procedure) was done within 12 weeks before accrual. No previous therapy for prostate cancer was allowed. A performance status ⩽2, age <80 years, and a theoretical life expectancy exceeding 10 years were also mandatory. The following biological features were required: neutrophil count ⩾1500, platelets ⩾100,000, bilirubin ⩽ upper limit of normal (ULM), ALT and AST ⩽1.5 ULM and creatinine <140 μmol/L (or creatinine clearance >60 mL/min). A signed informed consent was required and the trial was approved by the National Ethics Committee (Comité de Protection des Personnes) and the local Institutional Review Boards (IRB).

Exclusion criteria were as follows: active infection, history of a thrombo-embolic event, uncontrolled cardiovascular comorbidity, contra-indication to aspirin, previous history of cancer, except basal-cell skin carcinoma and any disease incompatible with the planned treatment.

2.2. *Treatment schema (Fig. 1)*

2.2.1. *Endocrine therapy*

All patients were to be treated for 3 years with ADT using a luteinizing hormone-releasing hormone (LHRH) agonist (goserelin 10.8 mg every 3 months via a subcutaneous injection, as defined by a protocol amendment dated 15th April 2003), initially combined during the first 3 weeks with a peripheral anti-androgen.

2.2.2. *Local treatment*

The local treatment was to be decided in a multidisciplinary meeting (involving a radiotherapist, a urologist and a medical oncologist) prior to patient accrual (thus regardless of the allocated randomisation arm). The local treatment was to be performed 3 months after the initiation of systemic therapy. In patients with pN– prostate cancer, it could consist of radiotherapy or prostatectomy. In patients with pN+ disease, it could consist of radiotherapy or no local treatment. The decision was at the discretion of the multidisciplinary team, depending on local practices (for example regarding the use of radiation in patients with positive lymph nodes) or individual characteristics.

2.2.3. *Radiotherapy*

A 3D conformal technique was used according to recommendations from the GETUG group.[25]

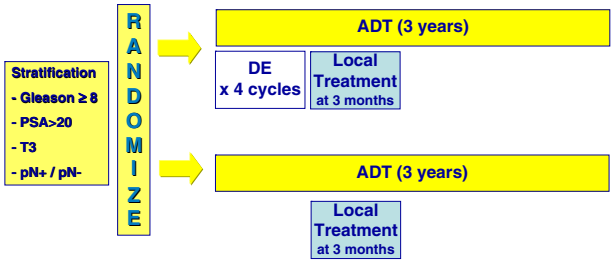

Fig. 1 – Trial design.

2.2.3.1. *Patient positioning*. Patients were treated in supine position. The patients had to empty the bladder and the rectum 1 h before the treatment-planning CT scan. Intravenous iodine contrast was required. A thin rectal catheter was used to improve the visibility of the anal canal. The treatment-planning CT scan was obtained from the sacroiliac joints to the lower edge of the lesser trochanters. The slice spacing was 3–5 mm.

2.2.3.2. *Target volumes*. In the first step, the clinical target volume (CTV1) included prostate and seminal vesicles, and in the second, the CTV was limited to prostate (CTV2). The planning target volumes PTV1 and PTV2 were obtained by adjunction of a 10-mm margin in all directions except posterior, where the margin was reduced to 5 mm to limit irradiation of the rectum. The delineation of the organs at risk was previously described.[25]

The indication of pelvic lymph nodes irradiation was optional in case of pN–. In case of pN+, the pelvis had to be irradiated if a local treatment using radiotherapy was decided. The upper limit of the pelvis could be either S1–S2 (small pelvis) or L5–S1 (large pelvis).

2.2.3.3. *3D treatment planning and dose*. Doses in PTV were specified at the International Commission on Radiation Units and Measurements point (ICRU 50 and ICRU 62).[26,27] The total dose was 46–50 Gy in the seminal vesicles (PTV2) and the pelvic lymph nodes (when irradiated), using a conformal 4-field technique. Several techniques could be used for the boost to the PTV2, including a 6-field technique with opposed lateral and four oblique, a 5-field technique with four oblique, and an anterior or posterior field, or eight regularly organised fields. The dose per fraction was 1.8 Gy or 2 Gy; 5 fractions per week. The treatment planning had to respect the organ at risk dose–volume constrains.[25] The photon energy of the beams should be at least 10MV. First-day port films or portal images of each field were required. Orthogonal images were verified on Days 2 and 3 and thereafter weekly.

The dose of radiotherapy delivered to PTV2 was originally set at 74 Gy (±4 Gy) in 2 Gy fractions. In 2005, the protocol was amended to require a dose between 74 and 78 Gy, based on the demonstrated evidence that a higher dose was associated with greater activity.[28–31] Avoiding rectal distension during CT planning was also recommended[32] to prevent the risk of local under-dosing.

2.2.4. *Prostatectomy*

Prostatectomy could be performed using either an open or a laparoscopic procedure. There was no specific recommendation about nerve sparing.

2.2.5. *Chemotherapy*

Docetaxel was given on day 2 at a dose of 70 mg/m^2, in a one-hour intravenous infusion, repeated every 3 weeks for four cycles. It was preceded by premedication with 50 mg prednisone the day before, 50 mg × 3 on the infusion day, and 50 mg × 2 the day after. Estramustine was given orally for five consecutive days, once every 3 weeks starting on day 1, at a dose of 10 mg/kg/day. Daily 300 mg aspirin was started on day 1 and stopped 3 weeks after the last cycle. The protocol

was amended on 16th September 2004 to include coumadin 2 mg daily, in case of a history of allergy to aspirin.

2.3. Surveillance

A visit to the oncologist was planned before each chemotherapy cycle with a blood cell count, creatinine, liver tests and serum PSA. Three months after systemic treatment was initiated the disease was re-staged by clinical examination, serum PSA and an ultrasound examination of the prostate. The patient was asked to fill in the EORTC QLQC-30 questionnaire, and then again, 1 year later. A clinical visit plus a serum PSA were then planned every 6 months. In case of a PSA rise, a repeated test was recommended 3 months later. If the criteria for biological progression were fulfilled, a CT scan of the abdomen and the pelvis and a bone scan were to be performed. Toxicity was assessed at each visit.

2.4. Statistical analysis

Continuous variables were expressed as median (range) and qualitative variables as incidences (percentages). PSA response rates and proportion of patients with hot flashes were compared between treatment arms by chi-square test. The analysis was performed in an intent-to-treat fashion. The primary endpoint of the trial is progression-free survival.

For quality of life analysis, the effect of treatment arm on quality of life scores adjusted on baseline score, age of patient and time of answer was evaluated using a logistic regression model. Of the 15 scores from the EORTC QLQ-C30 questionnaire, 7 items of interest were studied as follows: high quality score (>75 or $\leqslant$25 if items were symptoms) versus low or modest score ($\leqslant$75 or $\geqslant$25). The predictors were categorised as follows: treatment arm (ADT + DE versus ADT), baseline score ($\leqslant$75 versus >75 or >25 versus $\leqslant$25), age (<65 versus $\geqslant$65 years old) and time (month 3 and year 1).

All statistical analyses were performed using SAS software (Release 9.1; SAS Institute, Cary, NC, USA).

3. Results

From November 2002 to December 2006, 413 patients were accrued in 26 French centres. All but one patient had confirmed non-metastatic prostate cancer, while the remaining patient was found to have evidence of bone metastases. Three patients with a previous history of thrombosis and one patient with moderately elevated AST and ALT due to benign liver disease were accrued onto the trial with the approval of the principal investigator. One patient rapidly withdrew his consent after randomisation to the ADT + DE arm of the trial. Another patient who was randomised to the ADT arm received two cycles of DE by mistake (Fig. 2).

The median age was 63 years (47–77 years) in the two arms. The number of positive prostate biopsy specimens was 6 (range 1–23) and the percentage of positive biopsy specimens was 67% (8–100) in both arms. The distribution and number of stratification factors are described in Tables 1 and 2: 65% of the patients had at least two adverse prognostic factors.

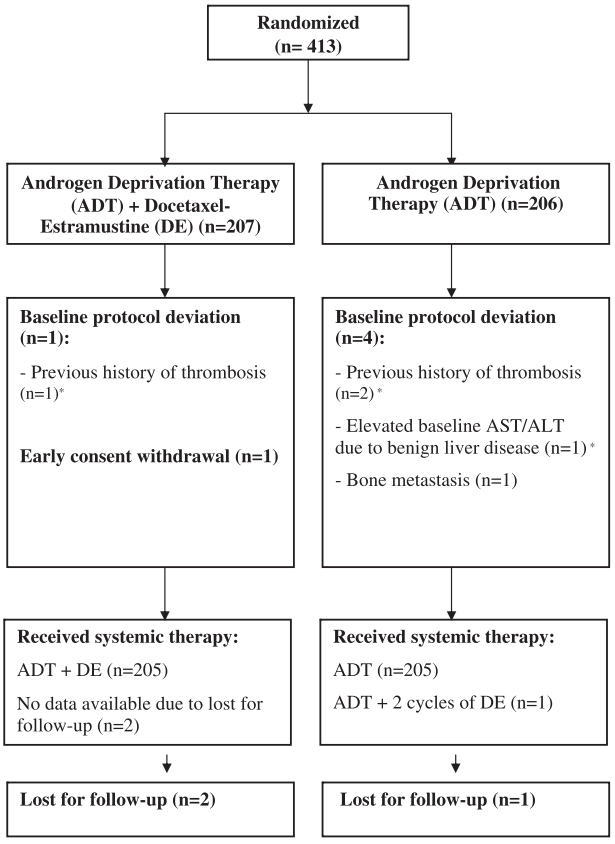

Fig. 2 – CONSORT schema (*: these patients were accrued after obtaining the agreement of the principal investigator because the baseline protocol deviations were deemed minor).

3.1. Treatment

In the chemotherapy arm, 95% of patients received the planned four cycles of docetaxel and 91% received the planned four cycles of estramustine.

The distribution of local treatments is summarised in Table 3. The local treatment consisted of the treatment planned at baseline before randomisation in 99% of cases. The median dose of radiotherapy was 74 Gy in both arms. A pelvic field was used in 105 (59%) and in 103 (58%) patients in the ADT + DE arm and in the ADT arm, respectively. A prostatectomy was performed in 25 patients and no pT0 was achieved.

As planned, the median duration of ADT actually received was 36 months in both arms.

3.2. Toxicity (Table 4)

Overall, chemotherapy was well-tolerated with severe toxicity occurring rarely. Only five patients (2%) developed a neutropenic fever. No patient required blood or platelet transfusion. There was no toxicity-related death. No patient in the ADT arm developed grade 3–4 toxicity during the three first months.

Table 1 – Stratification factors.

	ADT + DE arm $n = 207$	ADT arm $n = 206$
T1–T2	68 (33%)	67 (33%)
T3–T4	139 (67%)	139 (67%)
Gleason score		
4–7	120 (58%)	118 (57%)
8–10	87 (42%)	88 (43%)
Serum PSA		
⩽20 ng/mL	84 (41%)	85 (41%)
>20 ng/mL	123 (59%)	121 (59%)
Nodal status		
pN–	148 (71%)	146 (71%)
pN+	59 (29%)	60 (29%)

Table 2 – Number of adverse prognostic factors used for stratification.

	ADT + DE arm $n = 207$	ADT arm $n = 206$
Number of adverse prognostic factors		
1	71 (34%)	74 (36%)
2	90 (43%)	77 (37%)
3	31 (15%)	41 (20%)
4	15 (7%)	14 (7%)

Moderate to severe hot flashes were reported less often in the ADT + DE arm (2% versus 22%) during the first 3 months of systemic therapy.

By October 2010, 26 s cancers had been reported: 14 in the ADT arm, and 12 in the ADT + DE arm. No case of leukaemia or myelodysplasia was reported.

Long-term side effects of ADT, chemotherapy, radiotherapy and prostatectomy will be assessed when sufficient follow-up allows.

3.3. *Quality of life (Fig. 3)*

Quality of life was assessed at baseline, at 3 months (before local treatment), and then 1 year thereafter. Although chemotherapy initially had a negative impact on quality of life (global health status, $p = 0.01$; fatigue, $p = 0.003$; role functioning, $p = 0.003$; social functioning, $p = 0.006$), this effect had disappeared when re-assessed at 1 year. Chemotherapy had no significant impact on physical, emotional and cognitive functioning.

3.4. *PSA response (Fig. 4)*

The PSA response was assessed by measuring serum PSA 3 months after the initiation of systemic therapy (before local treatment): the median PSA value was 0.3 ng/mL (range 0.0–28 ng/mL) and 1 ng/mL (0.0–98 ng/mL) in the ADT + DE arm and in the ADT arm, respectively. A PSA response, defined as serum PSA ⩽0.2 ng/mL, was obtained in 34% and 15% of patients in the ADT + DE arm and in the ADT arm, respectively ($p < 0.0001$).

4. Discussion

Based on the original paradigm of breast cancer, the inclusion of chemotherapeutic agents known to be active in the metastatic setting in the multidisciplinary management of patients with localised cancers has been extended to the standard treatment of many neoplasms. It is now clearly established that taxane-based chemotherapy improves survival in patients with castration-resistant prostate cancer (CRPC) treated with first-line[22,23] and second-line[33] chemotherapy. There are the classic pro's and con's regarding the use of neo-adjuvant chemotherapy as compared to adjuvant chemotherapy.[34] In the present trial, several reasons led us to prefer the use of primary chemotherapy: (i) medical (endocrine) treatment is routinely initiated several months before radiotherapy, making it a practical window for associating another medical treatment, and (ii) it was thought that the neoadjuvant approach would also help optimise the dose-intensity of chemotherapy, without hampering that of radiotherapy. Indeed the observed dose-intensity of chemotherapy was excellent in this trial with more than 90% of patients receiving the planned chemotherapy. Similarly, the delivery of radiotherapy after chemotherapy was usually uneventful, with a median received dose of 74 Gy in both arms.

Studies evaluating the optimal timing of ADT with chemotherapy in LNCaP and in Shionogi preclinical models reported that mice receiving simultaneous treatments had a significantly longer time to progression versus sequential therapy,[35] while no difference was observed in MDA PCa2b xenografts.[36] Although the sequential use of chemotherapy and endocrine therapy is usually recommended in patients with breast cancer, no significant difference was observed in PFS or OS in a large phase III trial testing the two options.[37] Moreover, it is noteworthy that breast cancer most often concerns post-menopausal (endocrine-deprived) women, so that the sequential rather than concomitant rule mostly applies to the combination of anti-oestrogens (i.e. tamoxifen) and chemotherapy, and not necessarily to ADT and chemotherapy. Estramustine has demonstrated both hormonal and non-hormonal effects *in vivo*.[38] It inhibits microtubule function by

Table 3 – Local treatments.

	ADT + DE arm ($n = 207$)	ADT arm ($n = 206$)	Total ($n = 413$)
Radiotherapy	180 (87%)	178 (86%)	358 (87%)
Prostatectomy	10 (5%)	15 (7%)	25 (6%)
No local treatment	15 (7%)	12 (5%)	27 (6%)

Table 4 – Grade 3–4 toxicity in the chemotherapy arm.

	ADT + DE arm (n = 205)
Neutropenia	
Grade 3	29 (14%)
Grade 4	27 (13%)
Febrile neutropenia	5 (2%)
Grade 3–4 infection	4 (2%)
Grade 3–4 Thrombosis	5 (2%)
Grade 3 Diarrhoea	10 (5%)
Grade 3 Nausea	5 (2%)
Grade 3 Fatigue	5 (2%)
Grade 3 Alopecia	4 (2%)
Grade 3 Cardiac	2 (1%)
Grade 3 Skin	2 (1%)

binding to both tubulin[39,40] and microtubule-associated proteins[41] and was reported to increase docetaxel activity in CRPC.[42] This was the rationale for selecting docetaxel–estramustine, rather than single agent docetaxel, as the chemotherapy regimen in this trial. However, in the absence of a sufficiently powered randomised trial, debates continue over whether combining estramustine with chemotherapy improves survival in patients with CRPC, even though a recent meta-analysis suggested an improvement of both PFS and OS.[43]

The DE regimen was generally well tolerated with no toxicity-related death and a febrile neutropenia rate of only 2%. The thrombo-embolic event rate was also low (2%), in marked contrast with the high rate (12%) reported in the RTOG 99-02 trial testing paclitaxel, etoposide and estramustine in a similar population of patients.[44] The better tolerance profile observed in the GETUG 12 trial could be due to aspirin prophylaxis, the difference in the estramustine schedule (5 days in GETUG 12 versus 14 days in RTOG 99-02), the use of other chemotherapy agents, and a potential effect of pelvic radiotherapy on vessels (radiotherapy was used before chemotherapy in RTOG 99-02). Hot flashes were reported less often in the ADT + DE arm (2% versus 22%, $p < 0.001$) during the first 3 months, indicating a potential inhibiting effect of chemotherapy. Previous trials testing mitoxantrone or etoposide-containing regimens in early-stage prostate cancer reported an increased incidence of secondary leukaemias.[44,45] Reassuringly, in the present trial, no cases of leukaemia were reported, nor was an imbalance observed in second cancers, indicating that docetaxel and estramustine are unlikely to induce neoplasms. GETUG 12 is one of the first phase III trials to test chemotherapy with a report on quality of life data in patients with localised prostate cancer. Only a moderate detrimental effect was observed 3 months after the initiation of therapy, and this effect was shown to be reversible when reassessed 1 year later, indicating that chemotherapy does not impair quality of life indefinitely.

As long-term follow-up is required to assess the outcome of patients with localised prostate cancer, early surrogate endpoints for PFS and OS are needed. In this setting, several groups have underlined the strong association between an early major serum PSA decline (with cut-off of 0.1, 0.2, and 0.5 ng/mL) and a favourable outcome.[46–48] Specifically, obtaining a PSA of less

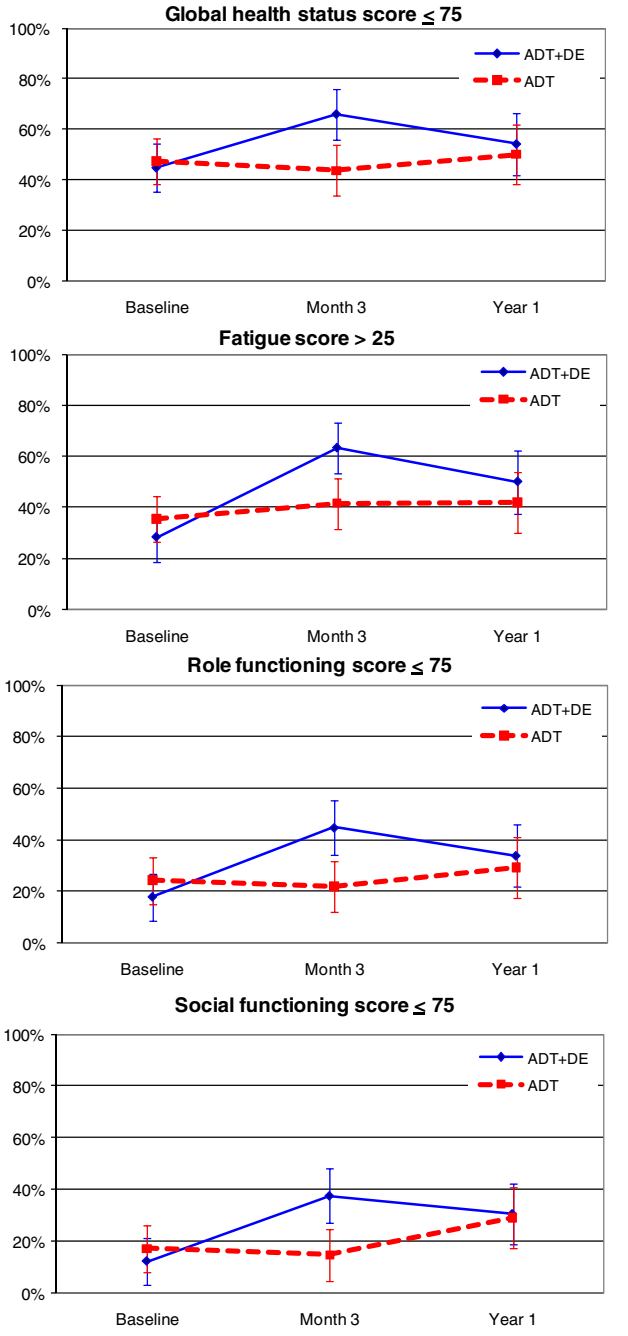

Fig. 3 – Quality of life.

than 0.2 ng/mL 3 months after the initiation of ADT and before radiotherapy was shown to be predictive for clinical PFS: the 10-year clinical relapse-free probability was 100% and 45%, respectively ($p = 0.02$).[47] In the GETUG 12 trial, a PSA level ⩽0.2 ng/mL was obtained in 34% and in 15% in the ADT + DE and in ADT arms, respectively ($p < 0.0001$), which is a promising result, although a longer follow-up is warranted to assess whether this yields a benefit in PFS.

Only a few randomised trials testing chemotherapy in localised prostate cancer have been reported to date. In a phase III trial comprising 403 patients, longer PFS was reported with estramustine in pN+ patients, when compared with cyclophosphamide or observation,[49] although this effect

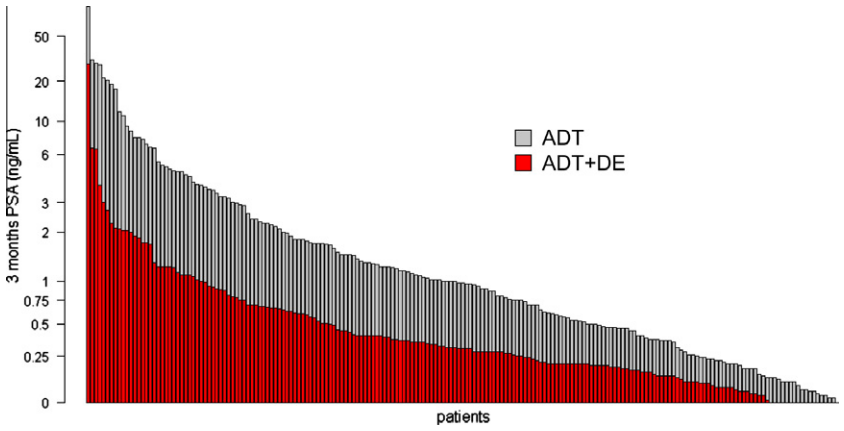

Fig. 4 – PSA response assessed at 3 months.

may be related to the endocrine properties of estramustine. In a randomised trial testing mitoxantrone plus ADT in 38 patients, an apparently significantly better outcome was reported in the chemotherapy arm, although the small number of patients prohibits any firm conclusions.[50] Investigators from the RTOG recently reported negative results of their phase III trial testing etoposide, paclitaxel and estramustine[51], while the results of the SWOG adjuvant trial testing mitoxantrone in 983 patients are still pending.[45] Approximately 10 ongoing phase III trials are testing whether a docetaxel-based regimen can improve patient outcomes in high-risk localised disease. Two or three of them have completed their planned accrual, including GETUG 12. Because the number of events (progression or death) has been less then expected so far, the Independent Data Monitoring Committee recommended that the survival (PFS and OS) analysis is performed when a median follow-up of approximately 7 years is reached.

Trial registration number

EU-20238, NCT00055731.

Conflict of interest statement

Pr. Karim Fizazi participated to advisory boards for Sanofi-Aventis, Astrazeneca and Keocyt, with no direct relationship with this trial.

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