Palliative treatment of endometrial cancer type 1 in elderly women with Anastrozole.

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Abstract

Purpose: Type I endometrial cancer is a common disease which takes place in female genital tract. The aim of the work is to asset the feasibility and safety of anastrozole in the palliative treatment of endometrial cancer in elderly women not eligible to standard surgical treatment.

Methods: eight patients with histological diagnosis of endometrial cancer were enrolled in this pilot study. Anastrozole was administered 1 mg daily per os after performing an accurate radiological mapping of the lesion. A questionnaire evaluated the quality of life of these patients.

Results: the median age was 85 (range 80-88years). The endometrial cancer was confined to the uterus in all patients. No progression of disease was observed. A partial response to the therapy was reported in seven patients, while no response was reported in one patient. A decrease in the symptoms such as pain, vaginal bleeding and vaginal discomfort was reported, as well as no progression of disease. The endometrial thickness after twelve months has showed a reduction of 9.25 ± 4.77 mm. The average rate of follow-up was 18.25 months. Four women died for other reasons, none of them related to endometrial cancer. Evaluation of symptoms showed a significant reduction of appetite loss and insomnia, while a significant increase of global health status and fatigue was reported.

Conclusion: our preliminary data reported that the palliative use of anastrozole may be a suitable therapy for a good control of early stages of endometrial cancer in inoperable elderly women, having a good compliance and tolerance.

Background

Endometrial cancer (EC) represents the most common gynaecologic malignant disease. It seems to occur in developed countries and especially in geriatric women; in fact, the mean age at diagnosis appears to be 68 years [1, 2]. Type 1 EC represents the most diffuse type (80–90% of all endometrial malignancy) and it is oestrogen-dependent. The endometrioid adenocarcinoma, another name of the EC type 1, is generally of low grade with a very favourable prognosis (5-years survival rate, in fact, is stated at about 83%) [3]. The persistent estrogenic stimulation of endometrial tissue, due to endogenous and exogenous ways, represents the main risk factor for the development of this malignancy. That being said, the most important risk factors include ovarian polycytosis, estrogenic hormonal therapy, an early menarche, a late menopause, tamoxifen therapy for the previous breast cancer, anovulatory cycles and obesity. In addition, the familiarity for endometrial cancer, Lynch's syndrome, hypertension, diabetes mellitus, and thyroid diseases are additional risk factors causing the onset of EC [4–8]. In post-menopausal women, the main source of oestrogen is represented by the peripheral aromatization of the steroids by the aromatase enzyme. This enzyme is present in many human tissues such as placenta, adipose tissue, skin, granulosa ovarian cells, skin fibroblasts, muscle, bone and brain. Furthermore, the activation and the transcription of this enzyme seems to be proportional in relation of the patient's age and body mass index. This phenomenon explains the rational of the increased risk of development of EC in the majority of obese
and elderly women, in post-menopause. Furthermore, the genic expression of the enzyme is significantly increased in the endometrial cancer tissue and it represents an index of tumour cell proliferation and growth [9–13]. The treatment of choice of endometrial cancer, for a woman in menopausal state, is the hysterectomy and bilateral salpingo-oophorectomy with minimally invasive surgery in combination with adjuvant chemotherapy and/or radiotherapy, in selected cases. The advanced age results in a decreased possibility for treatment of all malignant diseases, including gynaecological ones because some significant factors must be taken into account. For example, the health status, the comorbidities and the decay of the psycho-physical well-being are important limiting factors of any possible medical and surgical treatments. In particular, surgery procedures cause, in elderly patients, an increased rate of intra- and post-operative complications, nosocomial infections, lengthening of hospitalization, mortality and morbidity, with a resumption of quality of life.

Currently there are no guidelines which can determine the best therapeutic approach in the treatment of gynaecological malignancies in elderly patients. In fact, there are several therapeutic approaches such as chemotherapy, hormone therapy and radiotherapy, but each one of them seems to mine in many different ways the quality of life of the patients, and the therapeutic goal must be reached by preserving all of these aspects. To our knowledge, based on current literature, there are no studies which focus on the use of aromatase inhibitors in the treatment of endometrial cancer in elderly patients. As it is shown in our previous review of the literature, aromatase inhibitors may have a possible benefit in the treatment of advanced/recurrence of type EC1.

The primary purpose of this study is to analyse the possible role of anastrozole in elderly patients who are not eligible for surgical treatment in terms of safety, efficacy, and clinical benefit. Secondarily to that, this study evaluates any possible progression of disease during drug therapy, any quality of life modifications due to toxicity and tolerability of the drug in this group of patients.

**Methods**

In this prospective study were enrolled 18 patients, with primary EC Type 1, Stage FIGO IA-IB, older than 75 years old, that were not candidate for surgical treatment because of the elderly age, general status and their comorbidities did not permit a traditional surgery. The exclusion criteria were represented by any possible radiological aspect of distant metastasis, ECOG performance status > 3, any previous and different neoplastic diseases in the previous 5 years, measurable disease by RECIST v 1.1, and no previous hormonal therapy for cancer. The present trial is approved by the Ethical committee of IRCCS Policlinico San Matteo in Pavia. Patients referring to our hospital for post-menopause vaginal bleeding were candidate to trans-vaginal ultrasound and endometrial biopsy during hysteroscopy. The histological examination reported in all patients’ endometrial cancer type I with oestrogen receptor (ER) and/or progesterone receptor (PR) positivity. A full clinical history, clinical examination, blood count, serum biochemistry was performed in order to analyse hepatic and renal function. All our patients underwent to abdomen and chest computed tomography (CT) in order to exclude distant or local tumour invasion, and pelvic magnetic resonance (MR) investigating the endometrial invasion by the tumour. In relation to the
general status of the patients each of them was proposed to undergo to palliative therapy with anastrozole in place of laparoscopic/laparotomic hysterectomy and bilateral salpingo-oophorectomy. Informed consent was obtained in order to protect the patients about off-label therapy. The anastrozole schedule was 1 mg/daily per os in order to minimize the adverse effect of progestagens, such as deep thrombosis. In according with National Health Service (NHS) Cancer Plan, the therapy was started within one month of diagnosis of EC [13]. Patients were treated with the same drug until disease progression, toxicity or death. Four month after starting the therapy, our patients underwent to ultrasound endometrial examination and abdomen CT in order to evaluate the response to the therapy. Tumour response was investigated and determined by using RECIST criteria. One month and four months after the first administration of the drug all the patients underwent to blood count and serum biochemistry evaluating the renal and liver functionality. Every six months the patients underwent to careful physical and transvaginal ultrasound examination of pelvic region and abdomen ultrasound or CT alternatively. In order to evaluate the quality of life in each of the patients which followed anastrozole treatment, the authors administered EORTC-QLQ30 questionnaire at different times: before starting the treatment, and six and twelve months after the treatment. The QLQ-C30 is based on five multi-item scales (physical, role, social, emotional and cognitive functioning) and nine single-items (pain, fatigue, financial status, appetite loss, nausea/vomiting, diarrhoea, constipation, sleep wellness and quality of life) [14]. The toxicity profile was established according to NCI CTCAE v 4.0. During follow-up the clinical response to the therapy was determined with WHO Handbook for Reporting Results of Cancer Treatment [15]. By RECIST 1.1, physical examination, and ultrasound evaluation: complete response (CR) when all disease lesion disappeared. Partial response (PR) when the total cancer lesion size showed a decrease in size by 50% or more; progressive disease (PD) when the lesion increased by 25% or more in total measured size; Not changed (NC) when it was not possible to establish the reduction of tumour lesion by 50% or more. The present trial adheres to CONSORT guidelines.

**Statistical analysis**

All of our data were expressed in term of median value and ranges. Response to the therapy was described in terms of reduction of endometrial thickness, vaginal bleeding.

Subscales of EORTC-QLQ30 questionnaire have been calculated following the manual instructions; change of subscale scores at 6 and 12 months with respect to baseline were evaluated fitting population-averaged generalized equation models.

**Results**

Eight patients, according with inclusion criteria, were enrolled in the present study between 2015 and 2018, while ten women were excluded, as showed in the flow chart (figure 1). At the time of enrolment, the mean patients age was 85 ± 2.61 years (range 80-88 years). All patients have a diagnosis of endometrial cancer stage IA/IB, according with FIGO system 2009. The histological and immunochemistry analysis demonstrated endometrial cancer type 1 in all patients (table 1). All eight of them were candidate to
pharmacological therapy without any previous treatment. No one was candidate to surgical treatment in consideration of age and comorbidity (ECOG < 3). Before starting the treatment, pelvic ultrasound, CT scan and Pelvic RM evaluated the lesion mapping: in all patients the tumour appeared confined to the uterus. No one of the patients had at baseline abdominal or chest lesions. All patients received the same treatment: anastrozole 1 mg/ die per os. The response to the therapy after six and twelve months was observed. We defined response as a reduction in endometrial thickness by instrumental evaluation. Partial response was observed in seven patients (87.5%). A decrease in the symptoms such as pain, vaginal bleeding, and vaginal discomfort was reported, as well as no progression of disease. In one patient the endometrial thickness did not change significantly (12.5%), and she referred a persistence in vaginal bleeding, pain and vaginal discomfort during follow-up. Moreover, no progression of disease was reported. The average follow-up was 18.5 ± 5.2 months (mean ± SD). The endometrial thickness after twelve months had a mean of 10.74 ± 4.68 mm, with a reduction of 9.25 ± 4.77 mm (relative reduction of 44%) (table 2). Four women died for other reasons during the follow-up: two patients died for heart failure following previous history of myocardial ischemia, one woman died after complicated femur fracture, another one died after accidental fall, and another one after complications caused by pneumonia. None of them related to endometrial cancer, disease progression/relapse or therapy side effects. Toxicity data were available for all patients included in the present trial. All of the patients did not report any common side effects of the drugs after starting the therapy and/or during the follow-up such as vomit, diarrhoea, alopecia, skin rashes, fever, except occasional nausea (50%), muscle/joint aches and bone pain (62.5%), or fatigue (62.5%) during the first months of the treatment. No toxicity of grade 3-4 was declared. The compliance with the therapy was reported in consideration of a decrease in vaginal bleeding, subjective well-being, and easiness of drug administration itself. No one of the patients had to stop the anastrozole therapy in consideration of the drug adverse effects. All the eight patients compiled the EORCT-QLQ 30 questionnaire before the beginning of the therapy, and at months 6 and 12 after the administration of drug. The global health status increased significantly twelve months after drug prescription (p=0.002) (figure 2a). However, fatigue increased significantly at six months (p=0.011) (figure 2 b). We also reported a significant decrease of appetite loss (p=0.038) at twelve months compared to the baseline (figure 2c). Insomnia decreased significantly six and twelve months after the administration of the therapy (p=0.008 and p=0.001, respectively) (figure 2d). No statistically significant changes from the baseline and follow-up were reported for other items of QLQ-C30. Table 3 reports the statistical meaning of the questionnaire items at baseline and after 6 and 12 months, reported by our patients.

Discussion

Aromatase enzyme is expressed significantly in endometrial stromal cells and it is physiologically responsible of the oestrogens synthesis; it induces, in consideration of its expression, the proliferation of tumour cells, and this phenomenon leads to the transformation of neoplastic tissue [16]. Aromatase inhibitors cause a block of the activity of the aromatase cytocrome p-450 enzyme by binding the heme group, which leads to a decrease of the oestrogens synthesis and blood concentrations. Aromatase inhibitors play a significant role in post-menopause, when the gonadic oestrogens have low blood-
concentration due to the inactivity of hypothalamic-pituitary-ovarian axis. In all post-menopausal women, the reduction of the conversion of testosterone to oestrogen decreases by 90% [17]. Anastrozole is a non-steroidal aromatase inhibitor of third-generation, which is able to bind the enzyme with a reversible mechanism, hence inhibiting it completely (99% of the enzyme activity appears to be blocked) [17, 18]. However, as our previous literature review showed, the use of aromatase inhibitors has a moderate clinical benefit in case of recurrent/advanced EC [19]. Nevertheless, the work of Gao et al., demonstrated that the use of aromatase inhibitors appears to be a possible therapy in endometrial cancer in early stages, based on the literature review of previously data [20]. Also Thangavelu et al. demonstrated that the markers of proliferation (KI-67 protein) and apoptosis (bcl2 protein) decrease in those patients with EC which underwent to anastrozole as a neoadjuvant therapy [21]. These considerations are the biological and biochemical bases for the rational of the administration of anastrozole in aged women, not suitable for surgery. In fact, the EC type 1 is commonly diagnosed in early stages in several patients; nevertheless, there is a group of patients in which surgical treatment (which is a better therapeutic option in this stage of disease) is not feasible for different reasons such as advanced age and comorbidities. In these cases, the neoadjuvant/palliative therapy is the best therapeutic option for these patients, in order to give them an alternative therapy for the management of the symptoms of EC.

Our preliminary trial shows that anastrozole can be a valid therapeutic option as a palliative therapy in the treatment of EC in elderly women which improves not only the quality of life of these patients, but also helps them to relieve the disease-related symptoms. Anastrozole administration appears to be effective as a palliative therapy in all of the patients enrolled in our trial with EC type 1. In fact, this treatment causes a good clinical response in 87.5% of the cases (the patients died for other reasons were included) and only one patient demonstrated stable disease. Moreover, the treatment allowed a good control of endometrial disease without any need for surgery intervention, which would have been difficult in relation to the patients’ advanced age and frequently present co-morbidities. Anastrozole therapy may prevent the onset of further recurrences and the progression of endometrial cancer. Physical well-being and compliance to the therapy was evident in all of our patients, in relation to a well-tolerated therapy and a low report of side effects in this particular category of elderly women. In fact, the hormone therapy resulted in a subjective well-being and an easiness of administration which are both important aspects to consider in all aged patients. As the QLQ-C30 questionnaire reported, the global health increased significantly twelve months after beginning the therapy, which highlighted the clinical benefit of this palliative therapy for elderly women with EC. The global improvement and the reduction of the symptoms (especially vaginal bleeding) are associated with a radiological and physical response to the therapy, also in case of a stable disease. The psychological and physical benefit of this therapy, in our opinion, also regards the wellness of the sleep with a decrease of insomnia at six and twelve months. The significant increase of appetite loss and fatigue, according to our opinion, are not related to the side effects of the therapy with anastrozole, but could more likely be related to the age of the patient; in fact, the women enrolled in this study were very aged patients, in which it is known that the sense of fatigue and the appetite decrease are typical of this age. The unchanged values reported in the other items of questionnaire are probably related to the early stage of disease. In fact, EC being confined to the uterus,
does not cause significant appearance of pain or clinical manifestations which cause distress in the patient. The use of anastrozole also permits to avoid the risk of surgery in elderly women. Laparoscopic or laparotomic hysterectomy with bilateral salpingo-oophorectomy is possibly associated with delayed healing, lymphedema, infection, haemorrhages, and an increase of hospitalization and post-operative complications. Nevertheless, the rate of surgery in patients aged more than 80 years is similar of the one stated in younger women [22]. Any possible complications of surgical procedure in older women decrease their quality of life, especially in women with several comorbidities [23].

In according with Valenzano Menada et al. [24], endometrial thickness during the administration of anastrozole decreased significantly and the mean reduction was 4.5 mm in those patients with previous breast cancer treated with anastrozole and tamoxifen, while in our case the volume reduction of endometrial thickness was 9.25 mm. Probably this value can be related to a different endometrial tissue considered in these trials. In our opinion the endometrial cancer cell, in which the aromatase enzyme is active, has a better response and reports a significant reduction in its volume, especially considering those patients who did not assume any previous hormonal therapy, which may influence the biological mechanisms of endometrial growth.

However, it’s important to highlight that the surgery in elderly women is not contraindicated only by age factor, in relation to its potential benefit [25]. Mini-invasive surgery and robotic laparoscopy demonstrated a large benefit in elderly women in terms of reduction of complications [26, 27]. Also, in consideration of any possible role of neoadiuvant chemotherapy and radiotherapy, Eggeman et al., [28] in their work, described that elderly women with EC generally refuse this kind of treatment because radiotherapy and chemotherapy are not recommended by the physicians, in relation of performance status and medical diseases of the patients.

The use of anastrozole also decreases the risks of surgery and the adverse effects of other hormonal therapy, such as megestrol acetate, and neoadiuvant chemotherapy or radiotherapy, and it appears an easy and safe palliative therapy also in case of symptomatic women with a short life expectancy; these data confirm that the therapy is acceptable in elderly women and it can prove to be beneficial in those patients with the same conditions. Also, the use of aromatase therapy may be preferable due to the comorbidity typical of advanced age and also less adverse effects, which appear to be fewer than other hormonal therapies. The benefits of levonorgestrol releasing IUS system (Mirena) demonstrated the efficacy in the treatment of EC and in the decrease of malignancies progression in those patients which were at high risk for surgical procedure [29]. However, the use of oral therapy deletes the discomfort caused by the insertion of IUS system, and the possible incompliance by aged women for this kind of medical dispositive. Considering progestagens for the treatment of endometrial cancer, their role is known since 1950s. These drugs appear to have an anti-oestrogen activity by decreasing ER, by increasing oestrogen dehydrogenase enzyme, and by blocking the production of new receptors in endometrial tissue [30]. In case of endometrial cancer, the use of progestagens, such as medroxyprogesterone acetate approved by FDA, demonstrated to facilitate a regression in EC (60–70% of cases) [31, 32]. However, several sides effects are reported by the use of these drugs, such as weight gain, hypertension, oedema,
increases of blood sugar level, sleeps discomfort, tremor, bowel disturbance, and the most dangerous adverse effects such as thrombosis and pulmonary emboli [32, 33]. Further trials should be focused to relate the use of aromatase inhibitors and progestin therapy in the endometrial cancer treatment.

The most important limit of our study was the small sample of women enrolled in this pilot study. Nevertheless, the prolonged follow-up of these patients demonstrated that this therapy is an interesting palliative option in all patients not eligible to the standard therapy, and this data is supported by the safety, easiness of administration and the good compliance reported by all our patients. Moreover, another weak point of this study is the application of EORTC-QLQC30 in aged women; in fact, the accuracy of this questionnaire probably lapses in the case of very elderly patients because many items are either interpreted in relation of the pathological and physical conditions of the patients and do not reflect the real condition of the woman. Furthermore, larger and multicentric studies are necessary to confirm our data.

**Conclusions**

In conclusion, the mini invasive surgery appears to be the best option in elderly women for the treatment of EC. Nevertheless, in those patients with reduced life expectancy, the primary goal of palliative therapy of EC is to reach a good control of cancer symptoms, good tolerance of the therapy and an adequate quality of life: anastrozole may have all these characteristics.

**Abbreviations**

EC  
Endometrial Cancer  
ER  
oestrogen receptor  
PR  
progesterone receptor  
CT  
computed Tomography  
MR  
magnetic resonance  
NHS  
National Health Service  
CR  
complete response  
PR  
partial response  
PD  
progression disease
Declarations

- Ethics approval and consent to participate:

The informed consent obtained was written.

The Ethical Committee of IRCCS Policlinico San Matteo in Pavia approved the trial

- Consent to publish: not applicable

- Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- Competing interests

The authors declare that they have no competing interests

- Funding

The authors declare that they have no founding to declare

- Authors’ Contributions

B Gardella project development
M Dominoni manuscript writing
S Bogliolo other formal analysis
C Cassani data collection
GV Carletti data collection
A De Silvestri data analysis
A Spinillo manuscript editing

- Acknowledgements

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References


### Tables

<table>
<thead>
<tr>
<th>Patients (age, years)</th>
<th>FIGO stage</th>
<th>comorbidity</th>
<th>ASA status</th>
<th>ER</th>
<th>PR</th>
<th>pain and vaginal bleeding before therapy</th>
<th>pain and vaginal bleeding at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (85)</td>
<td>IA</td>
<td>atrial fibris, arterial hypertension, venous insufficiency of lower limbs and thrombophlebitis, hypertrophic cardiomyopathy</td>
<td>4</td>
<td>positive</td>
<td>positive</td>
<td>referred</td>
<td>not referred</td>
</tr>
<tr>
<td>2 (80)</td>
<td>IB</td>
<td>Parkison disease, ischemic stroke, arterial hypertension, bronchial asthma</td>
<td>4</td>
<td>positive</td>
<td>positive</td>
<td>referred</td>
<td>referred</td>
</tr>
<tr>
<td>3 (86)</td>
<td>IA</td>
<td>heart attack, high blood pressure, diabetes mellitus, obesity</td>
<td>3</td>
<td>positive</td>
<td>positive</td>
<td>referred</td>
<td>not referred</td>
</tr>
<tr>
<td>4 (82)</td>
<td>IB</td>
<td>chronic obstructive pulmonary disease, diabetes mellitus, arterial hypertension, thrombophlebitis lower limbs</td>
<td>3</td>
<td>positive</td>
<td>positive</td>
<td>referred</td>
<td>not referred</td>
</tr>
<tr>
<td>5 (88)</td>
<td>IA</td>
<td>arterial hypertension, previous post-traumatic pneumotace, previous deep venous thrombosis</td>
<td>3</td>
<td>positive</td>
<td>positive</td>
<td>referred</td>
<td>not referred</td>
</tr>
<tr>
<td>6 (84)</td>
<td>IA</td>
<td>polymyalgia rheumatica, chronic pancreatitis, bilateral glaucoma, arterial hypertension, diabetes mellitus</td>
<td>3</td>
<td>positive</td>
<td>positive</td>
<td>referred</td>
<td>not referred</td>
</tr>
<tr>
<td>7 (87)</td>
<td>IA</td>
<td>thoracic aorta ectasia, arterial hypertension, diabetes mellitus</td>
<td>4</td>
<td>positive</td>
<td>positive</td>
<td>referred</td>
<td>not referred</td>
</tr>
<tr>
<td>8 (85)</td>
<td>IA</td>
<td>cerebral stroke, arterial hypertension, carotid atheromasis, obesity, diabetes mellitus</td>
<td>4</td>
<td>positive</td>
<td>positive</td>
<td>referred</td>
<td>not referred</td>
</tr>
</tbody>
</table>

Legend: ER oestrogen receptor, PR: progesterone receptor.

Table 1: demographic characteristics.
### Table 2: Endometrial Assessments

<table>
<thead>
<tr>
<th>Item</th>
<th>Duration of anastrozole treatments (months)</th>
<th>Endometrial thickness before therapy (mm)</th>
<th>Endometrial thickness at follow-up 12 months (mm)</th>
<th>Reduction of endometrial thickness (mm)</th>
<th>Relative reduction of endometrial thickness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD)</td>
<td>18.25 (± 5.20)</td>
<td>20.25 (± 7.92)</td>
<td>10.75 (± 4.68)</td>
<td>9.25 (± 4.77)</td>
<td>44.16 (± 19.5)</td>
</tr>
</tbody>
</table>

Legend: SD: standard deviation

### Table 3: EORTC-QLQ30 Items Results at Diagnosis and During Follow-Up

<table>
<thead>
<tr>
<th>Items</th>
<th>Baseline mean (±SD)</th>
<th>Six months mean (±SD)</th>
<th>Twelve months mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH (*)</td>
<td>64.58 (10.68)</td>
<td>69.79 (6.2)</td>
<td>76.04 (8.26)</td>
</tr>
<tr>
<td>PF</td>
<td>86.67 (11.27)</td>
<td>88.33 (9.92)</td>
<td>86.67 (10.69)</td>
</tr>
<tr>
<td>RF</td>
<td>97.92 (5.89)</td>
<td>100 (0)</td>
<td>93.75 (8.63)</td>
</tr>
<tr>
<td>EF</td>
<td>93.75 (7.39)</td>
<td>92.71 (5.34)</td>
<td>96.88 (6.2)</td>
</tr>
<tr>
<td>CF</td>
<td>100 (0)</td>
<td>95.83 (7.72)</td>
<td>97.92 (5.89)</td>
</tr>
<tr>
<td>SF</td>
<td>100 (0)</td>
<td>100 (0)</td>
<td>100 (0)</td>
</tr>
<tr>
<td>FA (*)</td>
<td>6.94 (8.27)</td>
<td>16.67 (14.55)</td>
<td>11.11 (11.88)</td>
</tr>
<tr>
<td>PA</td>
<td>8.33 (8.91)</td>
<td>6.25 (8.63)</td>
<td>2.08 (5.89)</td>
</tr>
<tr>
<td>DY</td>
<td>12.5 (17.25)</td>
<td>16.67 (17.82)</td>
<td>12.5 (17.25)</td>
</tr>
<tr>
<td>SL (*)</td>
<td>37.5 (27.82)</td>
<td>20.83 (24.8)</td>
<td>16.67 (17.82)</td>
</tr>
<tr>
<td>AP (*)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CO</td>
<td>8.33 (15.43)</td>
<td>0 (0)</td>
<td>8.33 (15.43)</td>
</tr>
<tr>
<td>DI</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>FI</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>


SD: Standard Deviation

Table 3 EORTC-QLQ30 items results at diagnosis and during follow-up.
Figure 1
Flow of patients through the present trial
Figure 2

Graphic representation of items of EORCT-QLQ30 with p value statically significant. Legend: (a) GH: Global health status; (b) FA: Fatigue, (c), AP: Appetite loss, (d) SL: Insomnia

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc