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ORIGINAL ARTICLE

Feasibility And Efficacy Of Letrozole In Heavily Pre-Treated Patients With Relapsed Ovarian Cancer Not Eligible For Further Chemotherapy Cycles

Short title: Letrozole in Relapsed Ovarian Cancer

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ABSTRACT

Objective. Ovarian cancer is the fourth most common cancer and the eighth leading cause of death due to cancer in women. People affected by ovarian cancer often experience relapses, and then need to be treated with various lines of treatment. The study aim was the effectiveness of letrozole in patients with relapsed advanced ovarian cancer already subjected to multiple lines of treatment (≥3) and chemotherapy was no longer the option of choice. The main outcome of our study was to evaluate Patients-Free-Survival (PFS). The secondary outcomes were the assessment of Overall Survival(OS), Treatment Free Interval(TFI), Quality-of-life(QoL) and treatment-related toxicities.

Materials and Methods. This is a case-control retrospective observational study. The patients who were included in the group of cases were those who took 1 tablet of Letrozole 2.5mg/day. The QoL was analyzed in terms of symptomatology, using the EORTC QLQ-C30 and QLQ-O28

Results. 40 patients were included: 20 were treated with Letrozole and 20 as controls. The average PFS in the treated group was similar to the control group (3.8vs2.7 months,p=0.39). The average OS in the treated group was superior to the control group (75vs48.6 months,p=0.07). The average TFI was significantly higher in the treated group than in the controls (10.3vs3.8 months,p=0.008). Analysis of the symptoms reported that were much more present in the control group than in the letrozole group.

Conclusions. Letrozole is associated with good PFS and increased OS in patients for which other chemotherapeutic options are no longer eligible. Other studies are needed to validate these preliminary results.

Key words

Letrozole; Ovarian cancer; Relapsed Ovarian Cancer; Chemotherapy.

INTRODUCTION

Ovarian cancer (OaC) is the fourth most common cancer and the eighth leading cause of death due to cancer in women [1]. Even though significant developments have been made in the last few decades, the rate of disease progression remains high: 80% of patients are estimated to experience a relapse within 18 months [2]. Recent literature considers it no longer OC as a single disease, but as a multi-factorial one [3]. Firstly, histology must be considered. OC can be divided into five histotypes: high-grade serous, low-grade serous, clear cell, endometrioid and mucinous. These histotypes represent distinct pathological entities, both clinically and molecularly [4]. Another important parameter is represented by the genetic profile of the patient and of the tumor itself, such as the mutations of the BRCA1 or BRCA2 genes [5-7].

Despite the numerous studies and the multiple therapeutic options introduced in recent years, the key treatment for this tumor remains, to date, platinum-based chemotherapy and the platinum-free therapy interval (Platinum Free Interval, PFI) is still the main prognostic factor in patients, both in terms of Overall Survival(OS) and Progression Free Survival(PFS) [2,8-13].

Unfortunately, the patients who will undergo a first relapse will almost inevitably have further recurrences. These patients often develop resistance to platinum-based chemotherapy (commonly used for the first two lines of treatment, at least) and will therefore have the need to perform additional lines of treatment [14,15]. Furthermore, the complications related to cumulative toxicity, due to the use of previous therapeutic lines, represent one of the main obstacles to treatment compliance [16].

In the literature, to date, there are no established oral maintenance treatments for patients with OC, apart from PARP-inhibitors, that are used in a different subsetting of patients, and Metronomic Cyclophosphamide, which hasn't shown excellent results [17-21].

The goal would be a maintenance therapy that is effective, convenient, well tolerated and with low cumulative toxicity.

Our case-control retrospective observational study analyzes this specific subsetting of patients, i.e. women with relapsed advanced OC already subjected to multiple lines of treatment (≥3) and in which chemotherapy was no longer the option of choice. These patients had maintenance therapy with aromatase inhibitors, as Letrozole. We evaluated the effectiveness and feasibility of this treatment, comparing it with a group of patients who did not perform any maintenance treatment. The primary outcome of our study is the PFS. The secondary outcomes are OS, Treatment Free Interval(TFI), Quality of Life(QoL) and evaluation of treatment-related toxicities.

MATERIALS AND METHODS

The data of patients with relapsed OC treated by the Department of Gynecology of the Campus Bio-Medico University Hospital of Rome in the period between October 2019 and January 2021 were analyzed.

All patients were included in the retrospective analysis based on inclusion and exclusion criteria.

The inclusion criteria were: age older than 18 years; the presence of high and low-grade OC recurrence (any histology); stage IIA-IV FIGO; patients underwent complete cytoreductive surgery; at least 3 lines of therapy already performed; platinum resistance or inability to perform other lines with platinum; inability to perform additional chemotherapy cycles; ECOG Performance Status≤2;

life expectancy over 3 months.
The exclusion criteria were: stage I FIGO; the presence of secondary neoplasia; decompensated psychiatric illnesses; patients unable to take oral therapy; platinum-sensitivity; ECOG Performance Status>2.
The study protocol was approved by the Ethics Committee of the Campus Bio-Medico University of Rome.

We analyzed the data relating to the follow-up visits the patients underwent every 6 months: gynaecological examination, tumour markers (CA125 and HE4) and total body CT. The patients who were included in the group of cases were those who took 1 tablet of Letrozole 2.5mg/day. In the treated patients we collected data from before the start of treatment and from follow-up visits. The minimum follow-up was 6 months, until June 2019. The mean follow-up was 6.4 months (range 6-20).

The main outcome of our study was to evaluate PFS. The secondary outcomes were the assessment of OS, QoL and treatment-related toxicities. PFS was calculated in months, from the start of the last treatment (in cases, from the start of Letrozole therapy) to the subsequent progression. The OS was calculated in months from the time of diagnosis until June 30, 2019, or until the patient's death. The QoL was analyzed in terms of symptomatology, using the EORTC QLQ-C30 and QLQ-O28 questionnaires, that evaluate different parameters such as asthenia, nausea, vomiting, swelling, abdominal pain, and limitations in daily activities.

For data analysis, we used the Wilcoxon two-sample test. Statistical significance was set at $p<0.05$.

RESULTS

Between October 2019 and January 2021, we evaluated women with advanced and progressing OC at the Campus Bio Medico University Hospital of Rome. According to the inclusion and exclusion criteria, 40 patients were included in the data analysis: 20 were treated with Letrozole 2.5 mg and 20 were taken as controls. The two groups were homogeneous. The characteristics of the patients are shown in Table 1. All of them underwent hystero-annessiectomy surgery and lymphadenectomy. Patients underwent 2 cytoreduction interventions on average (range 1-5).

In the experimental group, the prevalent histology was serous carcinoma, in 80% of cases (16/20 patients), as well as in the control group (90% of cases, 18/20 patients). In both groups, among the cases of serous carcinoma, the high grade was the most described (80%, 16/20 patients). In 70% of patients from both groups, the stage of disease was advanced (III C according to FIGO).

In two patients treated with Letrozole, the value of CA125 was not available at diagnosis. In all other patients in the experimental group, however, it was examined and the average value was 940.51 units/ml (range 47.30-6000). In the control group, the average value of the CA125 was 1403 units/ml (range 11-7520.5). 40% of patients (16/40) were tested for the BRCA genes mutation, which was present in 10% of cases (2 patients in each group).

In both groups, patients received standard Platinum-based chemotherapy 3-weekly as the first line of treatment. 80% of patients were sensitive to platinum, while 20% were platinum-resistant. In the experimental group, among the initially platinum-sensitive patients, 6/16 (37%) presented adverse reactions to Carboplatin, which led to an interruption of the drug: 2 patients switched to Cisplatin (then they interrupted it for the onset of renal failure), 2 switched to monotherapy with Taxol and 2 to PARP-inhibitor maintenance treatment. The others stopped platinum due to disease progression.

The patients underwent 6 different lines of adjuvant chemotherapy on average (range 3-10) before being treated with Letrozole.

Meanwhile, in the control group, 6 of the platinum-sensitive patients later showed adverse reactions to Carboplatin and changed chemotherapy patterns. The average of therapeutic lines used was 4 (range 3-6). In 90% of patients, chemotherapy was the last type of treatment undertaken. The association Cyclophosphamide + Methotrexate (with a PFS of 1 month) was used in 2 patients.

The average PFS in the group treated with Letrozole was 3.8 months (range 3-12), 18.3 weeks (range 12-52.6) and the average duration of treatment was 8.5 months (range 3-20) (Figure 1A, 1B). In 10 cases the interruption was due to the patient's death (50%), while in 2 cases (10%) it was due to the decision to switch to immunotherapy after disease progression. The other 8 patients (40%) were still on therapy at the time of the last follow up. The PFS in the control group was 2.7 months (range 3-16) ($p = 0.39$).

The average Overall Survival in the treated subjects was 75 months (range 20-137), compared to 48.6 months in the control group (range 3-124) ($p = 0.07$) (Figure 1C).

The average Treatment Free Interval, from the last chemotherapy cycle performed, was 10.3 months (range 3-29), significantly higher than the 3.8 months (range 3-16) in the controls ($p = 0.008$) (Figure 1D).

No patient treated with Letrozole stopped therapy because of the onset of toxicity.

Regarding haematological toxicity, no febrile neutropenies were found in the group treated with Letrozole and only 10% of patients (2/20) had grade G1 anemia. In the control group the most represented residual toxicity was anemia, present in 60% (12/20) of the patients (G2 20%, G3 20%, G4 10%), even at 4 months from the end of the last therapy, which left a residual leucopenia, still present after 6 months of follow up. 2 patients in the control group (10%) had an episode of febrile neutropenia one month after the end of chemotherapy treatment.

Analysis of the EORTC QLQ-C30 and QLQ-O28 questionnaires showed that 40% of patients treated with Letrozole presented asthenia (10%), nausea (10%) and thinning hair (20%) during treatment. Symptoms were much more present in the control group, with 60% of patients complaining asthenia, 30% nausea and vomiting, 40% constipation, 10% diarrhea, 30% abdominal pain, 30% swelling, 10% residual alopecia at 6 months (Table 2).

DISCUSSION

OC is the fourth most common tumour in women, after breast, cervix and uterine cancer. It represents the eighth cause of death due to cancer in women and in the United States is the most lethal form of gynecological neoplasia [1]. Even though numerous efforts have been made in recent years, the rate of disease progression remains high: 80% of patients experience a relapse within 18 months [2]. Consequently, in the natural history of the disease, it is common for patients to develop resistance to therapies, both platinum-based or other lines of treatment despite the introduction of immunotherapy [22].

In patients with OC in which chemotherapy is no longer one of the options of treatment, given the cumulative toxicity and poor compliance, the goal is to find a well-tolerated oral maintenance therapy that can allow to "control" the disease with low toxicity. The recurrence, even if you can't use more aggressive treatments, still deserves management, as a form of comfort for the patient,

too. In this subset, an oral therapy could be a good option, effective and convenient, without strongly affecting the quality of life.

Over the past two decades, a limited number of phase II trials investigated the use of Letrozole in various subtypes of OC, to treat relapses or as maintenance therapy. These studies are heterogeneous and they assessed PFS as the primary outcome and as the secondary outcomes OS, response to therapy based on CA125 values, complete and partial responses, stable disease, overall response rate and rate of clinical benefits. The side effects and quality of life were less valued.

In literature, the outcomes of these patients in terms of PFS have been very inhomogeneous, with a range from 2 to 64 months.

The studies that evaluated the use of Letrozole in a subset of patients with low-grade tumours are the ones that showed better results: Fader et al. and Gershenson et al. of 2012 and 2017, with a PFS respectively 82.8% at 2 years, 64.9 months and 61% at 6 months (Table 3) [23-25]. This best response in patients with low-grade serous tumours was confirmed in our study, in which patients with LGSC had an average PFS of 12 months vs 3.8 months in HGSC.

The response in high-grade tumours was also in line with what was present in the literature (Table 3). Bowman et al., in treating 60 patients with recurrence, showed an average PFS of 3 months [26]. In Papadimitriou et al., the PFS was 2.6 months [27]. In the study by Smyth et al., 11 patients who received Letrozole had stable disease for 6 months [28]. In the study by Heinzelmann-Schwarz et al., after 24 months of observation, 60% of the patients on treatment were without recurrence, compared to 38.5% of the control group [29].
The average PFS of our study was 3.8 months, a value in line with previous studies, that seems to confirm the benefit from the use of the drug even in this subset of patients.

The average OS was 75 months, in line with previous studies and greater than the one found in the control group (75 vs 48.6 months). This increase was not statistically significant, but it is very close to significance (with a p=0.07 and a limit of 0.05).

Significant values were obtained by comparing TFI (10.3vs3.8 months, p=0.008). This data was not evaluated in previous studies, but it appears to confirm the increased survival of patients in the terminal stages of the disease, when the chemotherapy schemes are no longer applicable.

In a sub-analysis, we evaluated the time elapsed from the last chemotherapy to the disease progression and in the treated group it was 6 months average (range 0-15), compared to 1.5 months (range 0-13) of the control group(p=0.0003). This is a statistically significant result, that seems to further support the effectiveness of Letrozole therapy in prolonging free time from disease progression.

Heavily pre-treated patients like those analyzed in this study commonly present important toxicities, linked to the numerous lines of chemotherapy they underwent, so it is good, in the search for a therapeutic alternative in terminal stages, to consider low-toxicity drugs. Haematological toxicities, for example, are very common in patients undergoing chemotherapy or treated with cyclophosphamide as maintenance therapy [30]. In patients treated with Letrozole, no serious side effects related to anaemia, thrombocytopenia and neutropenia were found, unlike what was seen in the control group (with G≥2 anaemia in 60% of cases).

At the moment, there are no studies evaluating QoL in patients undergoing Letrozole maintenance therapy. In our study, patients showed no alopecia, but only hair thinning in 20% of cases. Patients in the experimental group did not have vomiting, which was present in 30% of the controls.

In conclusion, the patients who took Letrozole were very adherent to the therapy, probably because it is an oral drug. The literature agrees in considering Letrozole a well-tolerated drug: the

side effects exist and were present in 40% of our patients, but they didn’t lead the patients to stop the drug [31].

Another important aspect is patients' perception during maintenance therapy: a study by Sehouli showed that patients expect from maintenance therapy an increased chance of recovery, a delay in tumour progression, an improvement in quality of life and few side effects [32]. These outcomes are aligned with our results.

The main biases of this study are the small number of patients evaluated, the retrospective and non-randomized nature of the study and the heterogeneity of the sample, which includes both low- and high-grade tumours.

CONCLUSIONS

Aromatase inhibitors, especially Letrozole, are emerging as a therapeutic option for patients with pure-relapsed and multi-treated OC, thanks to their low toxicity. The effectiveness appears evident in the last stages of the disease, in which other chemotherapeutic options are no longer eligible. The data showed a good PFS and an increased Overall Survival. Toxicity data showed that this treatment is feasible, and patients maintain a good quality of life. Therefore, the results of this study are encouraging, but studies with a larger, prospective, randomized sample are needed to validate these preliminary results.

Actually, a randomized phase III trial (NCT04421547) is ongoing to evaluate the efficacy of Letrozole in heavily pretreated recurrent OC patients, we are awaiting the end of accrual and results.
In the future, interesting results could be obtained by dividing patients with high- and low-grade tumors and evaluating the status of hormone receptors, to understand which subset of patients could benefit from this treatment.

COMPLIANCE WITH ETHICAL STANDARDS

Author Contributions:

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Ethical Approval: Considering the retrospective nature of the study (observational and not interventional, no randomization was made) not approval by our IRB was requested. Approval was granted by the University “Campus Bio-Medico” of Rome. This study was conducted following the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1946).

Informed consent: The enrolled patients gave their informed consent to the study.

Data sharing: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. Patients characteristics and treatment details.

	Letrozole (n=20)	**Controls (n=20)**
Age, average in years (range)	61.2 (41-78)	67,8 (48-79)
Histology, n(%)		
• **Serous Carcinoma**	16 (80)	18 (90)
• **Endometrioid Carcinoma**	1 (5)	1 (5)
• **Transitional Carcinoma**	1 (5)	1 (5)
• **Mixed Mesodermal Carcinosarcoma of the Ovary**	2 (10)	0
Grade, n (%)		
• **High grade (G3)**	16 (80)	16 (80)
• **Low grade (G1)**	2 (10)	2 (10)
• **X Grade**	2 (10)	2 (10)
Stage (FIGO), n(%)		
• **II B**	2 (10)	0
• **III B**	2 (10)	2 (10)
• **III C**	14 (70)	14 (70)
• **IV**	2 (10)	0
CA125 at diagnosis, in unit/ml		
• **Average (range)**	940,51 (47,30-6000)	1403 (11-7520,5)
Initial Type of Treatment		
• **CP3w, n (%)**	20 (100)	20 (100)
• **Cycles, average n (range)**	6 (3-11)	5 (3-6)
Lines of treatment, average n (range)	6 (3-10)	4 (3-6)
Primary cytoreductive surgery	20 (100)	20 (100)
• **Cytoreductions after the first one, average n (range)**	1 (0-2)	1 (0-4)
Residual cancer post-cytoreduction, n (%)		
• **R0**	16 (80)	18 (90)
• **R>1**	2 (10)	0

• **R>2**	2 (10)	2 (10)
BRCA, in %		
• **Positive**	2 (10)	2 (10)
• **Negative**	8 (40)	4 (20)
• **Not evaluated**	10 (50)	14 (70)

Table 2. Results for extra-haematological toxicity in Letrozole compared to control.

Extra-haematological toxicity	Letrozole (n=20)	Controls (n=20)
Asthenia, n (%)	2 (10)	12 (60)
Nausea, n (%)	2 (10)	6 (30)
Vomiting, n (%)	-	6 (30)
Constipation, n (%)	-	8 (40)
Diarrhea, n (%)	-	2 (10)
Abdominal pain, n (%)	-	6 (30)
Swelling, n (%)	-	6 (30)
Thinning hair , n (%)	4 (20)	-
Alopecia, n (%)	-	2 (10)

The TFI has statistical significance (significance set at p<0,05), *P value calculated with the Wilcoxon two-sample test.

Table 3. Studies compared by outcomes (with values).

	N patients	PFS	OS	I
Our study	20	3.8 months	75 months	0
Bowman 2002	60	3 months		3.3%
Papadimitriou 2004	27	2.6 months	26.7 months	4%
Smyth 2007	44	26% at 6 months		0
		5% at 2 years		
Fader 2017	15	82.8% at 2 years*	96.3% at 2 years*	
		79% at 3 years*	92.6% at 3 years*	
Gershenson 2012	33	61% a 6 months*	78.2 months*	
Gershenson 2017	38	64.9 months*	106.8 months*	13%
Heinzelmann-Schwarz 2018	23	60% at 2 years		6.4%

PFS = Progression Free Survival, OS = Overall Survival, I = Interruption of treatment due to side effects; * Fader e Gershenson (2012 and 2017) are studies that include different treatments and the values of PFS and OS are to be considered for the entire group that underwent hormonal therapy, not only Letrozole.

Figure 1: (A) Progression Free Survival in patients treated with Letrozole compared to control; B) Progression Free Survival in patients treated with Letrozole compared to control (weeks); C) Overall Survival in patients treated with Letrozole compared to control; D) Treatment Free Interval in patients treated with Letrozole compared to control.