

Expectations and preferences of patients with primary and relapsed ovarian cancer to maintenance therapy: A NOGGO/ENGOT-ov22 and GCIG survey (Expression IV)

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ABSTRACT

Background: Maintenance therapy induces remission and/or prolongs disease-free interval in primary and recurrent ovarian disease. For the treatment decision-making process, aspects of QoL and patients' preferences are crucial despite the fact that there are lacking scientific data. Therefore, we conducted this European-wide study in patients with ovarian cancer.

Methods: A 25-item questionnaire was provided to ovarian cancer patients via internet or paper-version in ten European countries (Austria, Belgium, France, Germany, Italy, Romania, Slovenia, Finland, Turkey and Spain). Data was captured regarding demographics, tumor stage, and therapy after first line and/or recurrent disease and about preferences of administration and expectations concerning maintenance therapy.

Results: Overall, 1954 patients participated from September 2013 to March 2016. A total of 42% had recurrent disease. A vast majority of patients (98%) with primary epithelial ovarian cancer underwent surgery followed by chemotherapy (91%). Almost one third of participants (29%) were under current maintenance therapy, whereas 45% had only heard of it. A total of 70% of patients with primary epithelial ovarian cancer heard about maintenance therapy from their doctor, 10% from other patients, and 8% from the internet. The main source of information about maintenance therapy in patients with relapsed epithelial ovarian cancer relapse was from the treating physician (72%), from other patients (8%), and from the internet (7%). For patients undergoing maintenance therapy, the four most disturbing adverse effects of maintenance therapy were polyneuropathy (37%), nausea (36%), loss of hair (34%), and/or vomiting (34%). The main objective of maintenance treatment, as perceived by patients, was to increase the chances of cure (73%), improvement of quality of life

(47%), and to delay tumor growth (37%). Many patients are willing to undergo maintenance therapy until tumor progression (38%) and 39% would prefer an oral administration. No significant and relevant differences have been detected in the cross-country sub-analysis regarding the expectations of maintenance therapy and between primary and relapsed ovarian cancer.

Conclusion:

Patients with ovarian cancer are willing to accept maintenance therapies of prolonged duration and prefer an oral administration. There is still a gap between efficacy of maintenance therapy and patient expectations. Patients need more information regarding adverse effects and treatment goals of maintenance therapy to avoid misunderstandings.

INTRODUCTION

Ovarian cancer is the leading cause of cancer-associated death and is furthermore associated with high disease and treatment-related morbidity,[1, 2]. The current therapeutic standard entails surgical cytoreduction followed by platinum-based chemotherapy. However, the majority of patients with advanced stage will recur. Besides tumor control, aspects of QoL (quality of life) are the main objective of cancer therapy,[2, 3].

More recently, new targeted therapies such as, anti-angiogenesis agents, such as bevacizumab,[4, 5] or PARP inhibitors (inhibitors of the enzyme poly ADP ribose polymerase), such as niraparib,[6], olaparib,[7] and rucaparib,[8] have been established as routine therapy in patients with epithelial ovarian cancer with a favorable impact on progression-free survival, while impact on overall survival is yet to be shown,[4-8]. Furthermore, no direct comparison of maintenance therapies has been analysed in randomized studies. Different studies have shown that patient

preferences and expectations may influence patient compliance and QoL,[9, 10]. Nevertheless, because there is lack of data regarding these aspects, we designed this international survey.

METHODS

The collected data are intended to serve as an instrument for a better understanding of patient needs and thereby improve compliance with therapy. The survey "Expression IV" is a concept of the working group "Supportive Therapies" of the North-Eastern German Society for Gynecological Oncology (www.NOGGGO.de) and has been conducted within the European Network for Gynaecological Oncological Trial Groups (<https://www.esgo.org/network/engot/>) and Gynaecologic Cancer Intergroup (www.GCIG.org). The questionnaires were reviewed by the study groups of the European Network of Gynaecological Oncological Trial Groups (ENGOT), were translated into the respective national languages by certified translators including a validation by a bilingual physician.

Adult in- and outpatients with ovarian, fallopian tube or primary peritoneal cancer (primary and recurrent disease) were invited to participate in this survey. The questionnaire was available as a paper version, as well as, online via www.expression4.net. Patients had both options and selected by personal preferences. With 25 questions, the questionnaire consisted of two parts: the basic sheet (patient's characteristics) and the progress sheet (communication with medical staff, patient's expectation and preferences regarding maintenance therapy). In an interdisciplinary workshop with gynaecologist, oncologists, statisticians, psychologists, nurses and representatives of self-help organization, the survey was implemented. Different studies on the topic were used as a basis for discussion and the questionnaire,[11, 12]. The questions could either be answered as a multiple

choice, free text or on a scale of 1-10. The survey was tested on 20 patients on comprehension and readability. The study was approved by each Charité ethic committees and the respective national ethic committees. The survey contained a brief explanation and information on the contents of the survey and data protection.

All results are presented as frequency and rate for categorical variables or median and range for continuous variables. Continuous variables were compared with the Kruskal-Wallis-test or the Mann-Whitney-U test, ordinal variables with the use of Kendall's tau b and categorical variables with use of the χ^2 . Nominal two-sided P values are reported, statistical significance set to $p < 0.05$. All data were analyzed using IBM® SPSS® Statistics release 23.0 (SPSS Inc. an IBM Company, Chicago, Illinois, USA).

RESULTS

A total of 1,954 participants from ten different countries were included in this study (Germany n=539 [27.6%], Turkey n=420 [21.5%], France n=371 [19%], Austria n=238 [12.2%], Slovenia n=147 [7.5%], Belgium n=122 [6.2%], Romania n=75 [3.8%], Italy n=32 [1.6%], Finland n=8 [0.4%], Spain n=2 [0.1%]). The majority of patients used the hard-copy version (96.2% hard-copy version vs. 2.8% online version). A total of 62% of the patients were between 51-70 years, 19.5% between 18-50 years, and 18.5% between 71-90 years. Pertaining to living scenarios, 18.3% stated to be living alone compared to 81.5% living accompanied.

While 32.1% of participants were not aware of their FIGO stage, 8.8 % were initially diagnosed with FIGO stage I, 5.5% FIGO stage II, 30.8% FIGO stage III, and 12.9% with FIGO stage IV. The majority of participants had primary ovarian cancer (51.9%) compared to 41.6% with recurrent disease, 6.5% were not evaluable for response(Table 1). Of all patients with recurrent disease, 53.9% reported of relapse

within 12 month after initial chemotherapy, 26.7% after 6 to 12 months, and 19.4% had a relapse within six months after chemotherapy. Almost all patients with primary epithelial ovarian cancer underwent primary debulking surgery (98.4%) followed by chemotherapy (90.7%), and 64.3 % stated to be under current therapy. Participants were asked about the regular intake of oral medications for comorbidities for non-cancer reasons. Two thirds (61.4%) reported to take tablets regularly (<3 tablets per day 30%; 3-5 tablets per day 18%; >5 tablets per day, 9%) and the majority of patients (90.3%) reported no issues regarding the intake. Of the 9.7% reporting problems, 23.4% stated that the tablets were 'too big', 23.4% 'too many', 16.9% reported 'forgetting to take' and the remaining 4.7% of patients 'did not believe in effect of the tablet'. Most patients described their health status under maintenance therapy as 'well' (35.2) or 'neutral' (34.7%), whereas only a few described their health status as 'bad' (8.1%) or 'very bad' (1.6%).

A total of 40.5% of patients with primary epithelial ovarian cancer reported having heard about maintenance therapy and 70.3% of these patients heard about maintenance therapy from doctors, 9.9% from other patients, 7.7% from the internet, 4.8% from television, 4.2% from pharmaceutical booklet, 3.6% from other sources, and 1.9% from relatives.

A total of 57.1% of the patients with relapsed epithelial ovarian cancer had heard about maintenance therapy and 71.5% of these patients had heard about maintenance therapy from doctors, 7.6% from other patients, 7.4% from the internet, 4.7% from television, 2.9% from pharmaceutical booklet, 4.0% from other sources and 1.8% from relatives.

Expectations of patients regarding maintenance therapy:

While 44.6% of the patients participating in this survey had heard about maintenance therapy, 29.3% were under current maintenance therapy. A total of 72.5% of patients would choose a maintenance therapy to 'increase the chance of cure', 46.6% to 'improve the quality of life' (QoL), 36.5% to 'delay tumor progression', 33.2% prefer 'no deterioration of QoL', 32.5% to 'shrink the tumour', and 25% to 'decrease CA125'. (Table 2) Most patients (38.4%) would accept to take maintenance therapy until tumor progression, 22.9% for 6-12 months, 7.7% for 12-18 months, 7.5% for 18-24 months, 2.9% for 24-36 months, and 7.1% for 48-60 months. (Table 3) Most patients would take an up to 24 months maintenance therapy if it leads to a delay in tumor progression by more than six months (53.3%), 9.9% of the patients did not want such a long therapy.

The preferred schedule of administration of maintenance therapy was daily oral (31.7%), followed by every three weeks by infusion (31.7%). (Table 4) The adverse effects of most concern in patients with ovarian cancer were polyneuropathy (36.7%), nausea (35.6%), loss of hair (34.0%), vomiting (33.7%), fatigue (25.2%), increased risk of infection (23.8%), edema (18.9%), high blood pressure (18.8%), increased risk of bleeding (15.6%), constipation (15.1%), diarrhea (13.1%), stomach ache (13.0%), skin rash or skin infections (9.9%), anaemia (9.2%), and wound healing disturbance (5.7%). (Table 5)

Maintenance vs. no maintenance

There was no significant difference seen regarding age ($p=0.56$), surgical therapy ($p=0.07$) or living situation ($p=0.42$) comparing patients choosing to obtain or not

obtain maintenance therapy. Patients with recurrent disease (38%) received significantly more often a maintenance therapy compared to patients receiving first line therapy ($p=0.001$; 38.3% vs. 28.7%). On the other hand, patients receiving maintenance therapy were significantly more often diagnosed with FIGO stage III or IV than with stage I-II at initial diagnosis ($p<0.001$, 60.9% vs. 6.6%). Patients under current maintenance therapy were willing to accept a longer maximal duration of treatment ($p=0.001$; 30.1% vs. 14.6%) and expected a higher chance of cure ($p<0.001$, 80.2% vs. 69.1%) compared to patients not under active therapy.

Results ≤ 70 vs. > 70 years of age

Patients older than 70 years were significantly more often not aware of their initial tumour stage ($p=0.001$; 49.7% vs. 32.7%) and underwent surgery significantly less often ($p<0.001$; 92.4% vs. 97%), while no differences were seen regarding the administration of chemotherapy ($p=0.075$; 96.4% vs. 93.9%). Older patients collectively stated to be living alone significantly more often ($p<0.001$; 32% vs. 15.1%) and to take significantly more tablets for co-morbidities than younger patients ($p<0.001$; 81.8% vs. 57.1%). There was no significant difference seen for obtaining maintenance therapy ($p=1.0$; 33.6% vs. 33.4%) and the acceptable maximum duration ($p=0.601$; 26.3% vs. 26.4%) between older or younger patients. More patients under 70 years stated to have heard about maintenance therapy ($p=0.023$; 49.6% vs. 42.6%). There was a significant difference regarding the most important goals of maintenance therapy between the two age groups. Younger patients highlight the importance of increased chance of cure ($p=0.036$; 59% vs. 52.3%), while older patients prefer no deterioration of quality of life (QoL) ($p=0.002$; 17% vs. 10.4%). There was no significant difference in the preference for administration of

maintenance therapy between these two groups ($p=0.079$; 32.5% vs. 29.7%).

Regarding the adverse effects older patients were more concerned about high blood pressure ($p=0.003$; 24.8% vs. 17.5%), while younger patients were more concerned about the increased risk of bleeding ($p=0.013$; 16.6% vs. 11%), vomiting ($p=0.003$; 35.2% vs. 26.6%), as well as wound healing disturbances ($p=0.007$; 6.3% vs. 2.5%).

Primary vs. recurrent disease setting

Significantly more patients with primary ovarian cancer stated to feel 'very well' when asked about their current state of health (27.9% vs. 10.9%; $p<0.001$), while significantly more patients with recurrent disease were taking tablets for co-morbidities regularly (66% vs. 57.4%; $p<0.001$). Patients with relapsed disease were more aware of the concept of maintenance therapy than patients with primary epithelial ovarian cancer (57.1% vs. 40.5%; $p<0.001$). Regarding the question of the most important goal of maintenance therapy, patients with recurrent disease were more often expecting 'shrinking of the tumour' (11.2% vs. 7.4%; $p=0.005$), 'decrease of CA125' (7.5% vs. 2.5%; $p<0.001$), and a 'delay of tumor progression' (17.7% vs. 6.2%; $p<0.001$). Conversely, patients with primary epithelial ovarian cancer more often expected an increased 'chance of cure' (61.8% vs. 51.6%; $p=0.006$).

Significantly more patients with recurrent disease were willing to take maintenance therapy until tumor progression (52.6% vs. 40.4%; $p<0.001$). There was no significant difference seen in preference for administration of maintenance therapy ($p=0.22$), while patients with recurrent disease were more often worried about constipation ($p=0.04$) and edema ($p=0.005$) compared patients in remission.

Comedication vs. no oral medications

Patients without a regular intake of oral medications described their health status more often as 'very well' (27.5% vs. 13.2%; $p < 0.001$) and were willing to accept maximum duration of maintenance therapy 'just for 6-12 month' compared with patients with regular intake of oral medications (31.3% vs. 22.9%; $p = 0.001$).

Participant with regular intake of oral medications more often preferred an oral administration of maintenance therapy (45.2% vs. 38.9%), as well as a daily (oral) schedule (34.1% vs. 26.9 %).

DISCUSSION

Maintenance therapy has a crucial role in treatment of primary and relapsed ovarian cancer). Several studies are ongoing to evaluate other maintenance therapies, monotherapy or in combination, such as immune checkpoint inhibitors,[13], and inhibitor of VEGF signalling,[14]. However, trials show different adverse effects, administration forms, schedules and comparators of available drugs for maintenance therapy,[5, 7, 15, 16, 17, 18, 19, 20]. At the fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup in Tokyo, Japan, in November 2015, where representatives of 29 co-operative research groups studying gynecologic cancers gathered to establish international consensus on issues critical to the conduct of randomized trials, one of the recommended trial endpoints besides overall survival and progression free survival, was predefined patient reported outcomes and patient's preference,[3] This underlines the importance of our international survey. Within this survey, and for the first time in Europe, we explored

the expectations of patients with ovarian, fallopian tube and/or peritoneal cancer in various stages of treatment regarding maintenance therapy.

One of the positive signals of our survey is the fact that most patients place great value in their health status during maintenance therapy. Furthermore, patients with ovarian cancer also are highly motivated to accept maintenance therapies with a longer duration and most, prefer an oral form of administration. Patients with an existing oral medication intake are more willing to add another tablet to their daily routine, while patients without regular intake of tablets, prefer an intravenous administration of maintenance therapy. As already shown, in prior studies, co-medication and co-morbidity did not have an influence on overall survival or failure of chemotherapy,[21]. The above-mentioned facts depict the acceptance and compliance towards maintenance therapy by patients diagnosed with ovarian cancer, with no difference noted between the primary and relapse setting.

Regarding adverse effects, our study shows that patients are concerned about polyneuropathy, nausea and loss of hair. These are generally not associated with maintenance therapy, but rather with the primary treatment,[22]. This may offer an opportunity to improve communication between patients and physicians and to optimize management in general. As it pertains to different age groups in our survey, younger patients have higher expectations for full recovery. Concordant with the result of our European Expression-III- survey including a total of 1,830 patients with primary and relapsed ovarian cancer, a significant number of patients expect complete response from maintenance therapy, even patients with recurrent disease,[11]. These results show that there is still a gap between efficacy of maintenance therapy and patients' expectations.

There is an urgent need for more information regarding adverse effects and treatment goals of maintenance therapy to avoid misunderstandings and to increase

patient compliance. In addition to the already investigated parameters of maintenance therapy such as efficacy and tolerability, further trials should prospectively investigate the impact of patient expectations and preferences on toxicities and patient compliance. The information from our study should be discussed systematically with patients to increase compliance and satisfaction towards maintenance therapy in ovarian cancer. A recent study from Urkmez et al. underlines the importance of patient perception, expectations, experiences and the importance of being involved in the decision-making process of their treatments,[23]. Patient preference and expectations should also be followed within clinical trials with targeted therapies that focus on maintenance to understand their impact on patient quality of life and compliance.

Contributions

Jalid Sehouli and Irena Rohr designed the study. Irena Rohr wrote the first version of the manuscript. Michaela Heinrich and Rolf Richter performed the data analysis and interpretation. All authors participated in the interpretation of results, critically revised the paper and approved the final version to be published.

Acknowledgements

We thank all the patients, who made this study possible. This study has been presented on the ESCO annual meeting 2017.

Funding

The survey „Expression IV“ was supported by an unrestricted grant from Boehringer Ingelheim and Amgen.

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Table 1: Patients characteristics

	n= 1954 participants	All
Age	18-50 years 51-70 years 71-90 years	19.5 % 62.0 % 18.5 %
Stage of disease	Primary ovarian cancer Relapsed ovarian cancer Unknown	49.6 % 36.3 % 6.9 %
FIGO Stage at primary disease	I-II III-IV Unknown	14.3 % 43.7 % 32.1%
	Surgery	96.1%
	Chemotherapy	94.3 %
Current treatment	Yes No Unknown	64.3 % 35.0 % 0.7 %
Living situation	Not alone Alone	81.7 % 18.3 %
	Tablets for comorbidities	61.4 %
Maintenance therapy	Yes No No answer	29.3 % 57.9 % 12.8 %

Table 2. Estimation of current state of health

	n= 1954 participants	Percent
Very well	354	18.8%
Well	663	35.2
Neutral	678	34.7
Bad	159	8.1
Very bad	31	1.6
Missing data	69	3.5

Table 3. Personal objective to choose a maintenance therapy (multiple answers were allowed)

	n= 1782 participants	Percent
Increasing the chance of cure	1292	72.5
Improvement of QoL	831	46.6
Delaying the tumour progression	650	36.5
No deterioration of quality of life (QoL)	592	33.2
Shrinking the tumour	579	32.5
Decrease of CA-125	445	25
Other	85	4.8

Table 4. Acceptable maximum duration of maintenance therapy

	n= 1954 participants	Percent
6 – 12 months	447	22.9
12 -18 months	150	7.7
18- 24 months	146	7.5
24- 36 months	57	2.9
48-60 months	139	7.1
Until tumour progression	750	38.4
Missing data	265	13.6

Table 5. Delay in tomour progression

	n= 1954 participants	Percent
3 months	159	8.1
4 months	24	1.2
5 months	22	1.1
6 months	186	9.5
More than 6 months	1042	53.3
I don't want such a long therapy	194	9.9
Missing data	327	16.7

Table 6. Preference for administration of the maintenance therapy

	n= 1954 participants	Percent
Oral	754	38.6
I have no preference	563	28.8
Directly in the blood (intravenous)	439	22.5
No answer	198	10.1

Table 7. Preferred schedule of administration

	n= 1788 participants	Percent
Daily (oral)	567	31.7
Every three weeks (infusion)	562	31.4
Twice a day (oral)	278	15.5
Twice a week (oral)	227	12.7
Weekly (infusion)	122	6.8
Other schedule	32	1.8

Table 8. Most concern side effects

	n= 1810 participants	Percent
Polyneuropathy	664	36.7
Nausea	644	35.6
Loss of hair	615	34.0
Vomiting	610	33.7
Fatigue	457	25.2
Increased risk of infection (leukopenia)	430	23.8
Oedema	342	18.9
High blood pressure	340	18.8
Increased risk of bleeding (thrombocytopenia)	283	15.6
Constipation	274	15.1
Diarrhoea	238	13.1
Stomach ache	236	13.0
Skin rash or skin infections	180	9.9
Anaemia	167	9.2
Wound healing disturbance	103	5.7
Others	15	0.8