VIA MEDICA

REVIEW ARTICLE

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Treatment of advanced ovarian cancer with bevacizumab in Poland — a chance to improve survival still missed

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ABSTRACT

In Poland the use of bevacizumab, angiogenesis inhibitor, in the treatment of patients with advanced ovarian cancer is financed by the Ministry of Health within the existing Drug Program. Available data indicate that not all patients who could benefit from such a treatment finally receive it. There could be many different reasons for this situation — some are due to patients' clinical characteristics, but other result from misunderstanding of the eligibility criteria and the rules of the treatment program by physicians. The presented publication discusses comprehensively some oncological criteria that could be a subject of discussion, and which make qualification to bevacizumab-containing treatment more difficult.

Key words: ovarian cancer, bevacizumab, treatment program

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Introduction

Although availability of new targeted therapies has improved in Poland, the decision about their reimbursement from public resources is usually made more than one year later than in other EU countries. The development of innovative molecular therapies in gynaecological oncology is especially noticeable in patients with ovarian cancer, who represent a group with specific needs. This type of cancer is commonly asymptomatic for quite a long time, and there is a lack of efficient tools to diagnose it in its early stages, when there is a chance for the patients to be cured, whilst the prognosis in late stages is very poor. In Poland and western countries, the incidence of ovarian cancer already exceeds the incidence of cervical cancer [1]. Clinical trials conducted during last decade show the essential role of surgical treatment in patients with advanced ovarian cancer (OC), aimed at achieving complete cytoreduction. It needs specialised teams, with access to a properly equipped operating theatre. According to this, the introduction of advanced and extended cytoreductive operations faces major organisational and financial obstacles, and also depends on adequate experience and surgical technical skills.

The majority of patients with advanced OC still include women after suboptimal surgery as well as with distant metastases. The treatment patterns in this group have markedly changed in recent years. Two randomised clinical trials (RTCs) confirmed that neoadjuvant chemotherapy in this group of patients is not less effective than surgery [2, 3] and some other studies revealed the significant role of correct selection of patients with the intention to achieve complete cytoreduction to either primary surgery or neoadjuvant chemotherapy.

Reimbursement of bevacizumab treatment in Poland

Currently, therapy with bevacizumab is reimbursed in Poland in the first-line setting under the Drug Program

of the Ministry of Health (MoH) "Treatment of patients with advanced ovarian cancer (ICD10, C56, C57, C48)", Appendix B.50 (Tab. 1), hereinafter referred to as the "Program". This Program is dedicated to the patients with high risk of disease progression (*high-risk group*), identified in the ICON7 study [4], which was the only group achieving statistically significant benefits from bevacizumab in terms of overall survival. The "high-risk group" was more closely defined as patients meeting the following criteria:

— stage III, after suboptimal operation (residual disease after surgery ≥ 1 cm);
— all patients in stage IV;
— not operated patients in stage III.

In total, 248 such defined patients underwent the treatment with bevacizumab. Bevacizumab significantly improved overall survival (OS) by five months, being the very first new drug prolonging survival of OC patients since the introduction of paclitaxel in1996 [5].

A considerable advantage of bevacizumab is the possibility to use this drug during maintenance therapy. Because the maximal number of bevacizumab cycles is 18, it practically means that the patients after chemotherapy would receive the drug, potentially improving OS by 10–12 months. This is particularly important for the patients, giving them the feeling of continuous efforts against their disease instead of only follow-up, which in the high-risk group means actually waiting for progression.

According to the Polish National Cancer Registry there are about 3500 new cases of OC annually [1]. European literature data show that approximately 75% of them comprise patients in stage III and IV according to FIGO classification [6]. Based on the criteria of inclusion to the Program, at least 1400 (~50%) patients with advanced OC should be qualified to treatment with bevacizumab, improving OS in the high-risk group. However, MoH data from the Program realisation indicated in the first six months of 2016 only 545 patients (approximately 31% of all patients) received bevacizumab. It clearly means that each year more than 300 patients loose their chance for prolonged life.

Table 1 summarises detailed inclusion criteria in the Program; however, some technical aspects as well as the situations that require non-standard procedures raises some questions for treating physicians, so these should be more deeply analysed and discussed. Specifically, the terms with regards extension and timelines of surgical operation are not clear in the Program criteria.

This article comprehensively discusses oncological and surgical criteria for inclusion to bevacizumab treatment under the Drug Program "Treatment of patients with advanced ovarian cancer".

Organisation of bevacizumab treatment of patients with advanced ovarian cancer in Poland

According to the data from the National Health Found (NFZ), treatment within the Program was conducted in 65 institutions in our country (Tab. 2), that were mainly either clinical oncology or gynaecological oncology departments. The former treat the patients referred from surgical or gynaecological departments, potentially also from any other non-surgical department, with the capacity to diagnose OC. Patients in gynaecological oncology departments were operated on and received systematic treatment, including bevacizumab therapy. This seems to allow comprehensive analysis of OC treatment and better understanding of the criteria of inclusion to the Program, as well definitions regarding treatment with bevacizumab of OC patients.

Essential oncological definitions to understand the rules of inclusion of patients to the bevacizumab Program

1. Cytoreduction — surgical operation with the intention to remove cancer burden:
   a. complete cytoreduction, total (macroscopically) — no residual disease after operation;
   b. optimal cytoreduction — residual disease after operation < 1 cm in largest diameter;
   c. suboptimal cytoreduction — residual disease after operation ≥ 1 cm in largest diameter;
   d. primary cytoreduction — operation performed before chemotherapy;
   e. interval (delayed) cytoreduction — operation performed after neoadjuvant chemotherapy;
   f. exploratory laparotomy — surgical opening of the abdominal cavity aiming to assess disease stage, and taking the samples for histological evaluation.

   It is not completely clear whether the term "cytoreductive operation" should be considered as only laparotomy, performed with the intention of cancer resection, even if, due to disease advanced stage, only tissue specimen for histological evaluation is finally obtained. Exploratory laparoscopy, which allows to avoid unnecessary, suboptimal cytoreduction, seems to be more beneficial, less dangerous for patients, and equally efficient in identifying the high-risk group of patients, in whom achieving residual disease < 1 cm is not possible. It was supported by the results of international trials conducted in recent years [7, 8]. The Program does not include the definition of cytoreductive surgery; taking into account the fact that performing the exploratory laparotomy alone already qualifies the OC patient to the Pro-

Table 1. Drug Program Ministry of Health "Treatment of patients with advanced ovarian cancer (ICD-10C56, C57, C48)"

Scope of guaranteed service		
Beneficiaries	**Scheme of drug dosages in the Program**	**Diagnostic tests performed under the Program**
1. Treatment of patients with advanced ovarian cancer with use of active substance bevacizumab 1.1. Qualification criteria: 1) histological diagnosis of ovarian, fallopian tube, or primary peritoneal cancer 2) stage IV or II according to FIGO, with residual disease after operation > 1 cm (suboptimal cytoreduction; it is demanded to find the residual disease after operation with assessment of its size in cm) 3) no previous systemic treatment of ovarian cancer. Previous neoadjuvant chemotherapy is acceptable 4) performance status 0–1 according to Zubrod-WHO classification 5) age over 18 years 6) results of complete blood count with smear: a) platelet count higher than or equal to $1.5 \times 10^5/mm^3$ b) absolute neutrophil count higher than or equal to $1500/mm^3$ c) haemoglobin concentration higher than or equal to 10.0 g/dl 7) coagulology parameters: a) activated partial thromboplastin time (APTT) within normal range b) prothrombin time (PT) or international normalised ratio (INR) within normal range 8) liver and renal tests: a) total bilirubin concentration not exceeding 2-fold upper limit of normal (ULN) (except patients with Gilbert's syndrome) b) aminotransferase plasma levels (alanine and asparagine) not exceeding 5-fold ULN c) creatinine concentration within normal range	1. Carboplatin with paclitaxel: 1)carboplatin (AUC 5–6) — day 1 2)paclitaxel175 mg/m^2 — day 1 Rhythm: every 3 weeks, 6 cycles 2. Bevacizumab 7.5 mg/kg body weight intravenously on the infusion for 30–90 minutes — day 1 Rhythm: every 3 weeks, 18 cycles 1)patients receive bevacizumabin combination with 3-weekly chemotherapy cycles (maximum 6 cycles) 2)after cessation of chemotherapy the treatment is continued in 3-weekly cycles up to 18 cycles of bevacizumab treatment or disease progression or unacceptable toxicities (depending on what is first) 3)in cases when chemotherapy or one of its components is finished before completion of 6 cycles, treatment with bevacizumab could be continued according to the rules presented in point 2 4)bevacizumab will be administered from the first cycle of chemotherapy or from the second cycle if chemotherapy will be initiated before 28 days from major operation 5)in case of the need to stop the treatment with carboplatin, the drug could be replaced by cisplatin and treatment could be continued 6)in case of the need to perform a secondary operation it could be done no earlier than 28 days from administration of bevacizumab, and the further treatment with bevacizumab could be restored no earlier than 28 days after operation 7)modifications of dosage and rhythm of administration of particular drugs should be done according to approved Summary of Product Characteristics (SmPC)	1. Test during qualification to bevacizumab treatment: 1) histologically confirmed the diagnosis of ovarian, fallopian tube, or primary peritoneal cancer 2) complete blood count with smear 3) plasma level of: a) urea b) creatinine c) bilirubin 4) plasma level of aminotransferases (AspAT, AlAT) 5) activated partial thromboplastin time (APTT) 6) international normalised ratio (INR) or prothrombin time (PT) 7) plasma level of CA125 8) general urinalysis 9) pregnancy test — in women of child-bearing age 10) computed tomography of abdominal cavity and pelvis and other body areas depending on indications 11) computed tomography or nuclear magnetic resonance of the brain in case of clinical indications of metastases to central nervous system (CNS) 12) chest X-ray — in case of no CT scan 13) electrocardiogram (ECG) 14) blood pressure measurement 15) other tests according to clinical indications Postoperative (before initiation of bevacizumab treatment) computer tomography of abdominal cavity and pelvis should be done no earlier than four weeks after operations, but not later than two weeks after initiation of chemotherapy The aim of preliminary imaging evaluations is making possible later monitoring of disease progression

→

Table 1 (cont.). Drug Program Ministry of Health "Treatment of patients with advanced ovarian cancer (ICD-10C56, C57, C48)"

Scope of guaranteed service		
Beneficiaries	**Scheme of drug dosages in the Program**	**Diagnostric tests performed under the Program**
9) excluding pregnancy; 10) no contradictions to chemotherapy with carboplatin and paclitaxel 11) no contradictions to use bevacizumab, which are as follows: a) operation within less than 4 weeks since qualification to treatment b) active gastric or duodenal ulcer peptic disease c) unstable hypertension d) unstable ischaemic heart disease (IHD) e) previous cerebrovascular diseases f) congenital haemorrhagic diathesis or acquired coagulopathy g) diseases with increased risk of bleeding h) taking anticoagulants or antiplatelet (aggregants) drugs (excluding prophylactic doses) i) non-healing wounds j) proteinuria k) hypersensitivity to the active substances or to any of the excipients All criteria must be fulfilled cumulatively 1.2. Defining of treatment time under the Program Treatment is continued until the decision of treating physician about excluding the beneficiary from the Program, based on exclusion criteria 1.3. Exclusion criteria: 1) hypersensitivity to bevacizumab 2) administering of 18 cycles therapy with bevacizumab 3) disease progression during treatment 4) long-term adverse events of grade higher than or equal to 3 according WHO classification 5) persistent decreasing of performance status		2. Monitoring of safety of treatment with bevacizumab: 1) complete blood count with smear 2) plasma level of: a) creatinine b) bilirubin — in serum c) APTT and PT or INR 3) plasma level of aminotransferases(AspAT, AlAT) 4) general urinalysis 5) blood pressure measurement 6) other tests according to clinical indications The mentioned tests are performed every 3 weeks or before starting the next therapy cycle if drug administration was postponed 3. Monitoring the efficacy of treatment with bevacizumab: 1) computed tomography of relevant body areas according to clinical indications 2) assessment of CA125 plasma level 3) other tests according to clinical indications Imaging evaluations with computed tomography are performed: 1) after chemotherapy cessation 2) during bevacizumab treatment: no less often than every 24 weeks 3) at exclusion from the Program, unless for other reason than documented disease progression 4) at every increasing of CA125 plasma level more than 2-fold higher then nadir level 5) always if clinically indicated Assessments of CA125 plasma level are performed no less frequently than every 3 therapy cycles Treatment efficacy should be assessed according to RECIST criteria 4. Monitoring of Program realisation: The head of the NFZ keeps a registry of patients treated under the drug Program available via internet application

Table 2. Classification of ovarian cancer according to FIGO (version 2014) [8]

FIGO classification (version 2014)		
Stage I	**Tumour confined to ovaries or fallopian tubes**	
	IA	Tumour limited to 1 ovary or fallopian tube (capsule intact), no tumour on surface ovary or fallopian tube, negative peritoneal effusion or washings
	IB	Tumour limited to 2 ovaries or fallopian tubes (capsule intact), no tumour on surface ovary or fallopian tube, negative peritoneal effusion or washings
	IC	Tumour limited to 1 or 2 ovaries or fallopian tubes with:
	IC1	Surgical spill
	IC2	Capsule rupture before surgery or
	IC3	Tumour on surface ovary or fallopian tube, positive peritoneal effusion or washings
Stage II	**Tumour limited to ovaries or fallopian tubes with pelvic extension (below the pelvic brim) or primary peritoneal cancer**	
	IIA	Extension and/or implant on uterus and/or fallopian tubes
	IIB	Extension to other pelvic intraperitoneal tissues
Stage III	**Tumour involves 1 or both ovaries or fallopian tube/tubes or primary peritoneal cancer with spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes**	
	IIIA	Metastases only to retroperitoneal lymph nodes (cytologically or histologically confirmed)
	IIIA1	Metastases breadth in the largest dimension ≤ 10 mm
	IIIA2	Metastases breadth in the largest dimension >10 mm
	IIIA3	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
	IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm in the largest dimension ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen (without parenchyma)
	IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm in the largest dimension ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen (without parenchyma)
Stage IV	**Distant metastasis (excluding peritoneal metastasis)**	
	IVA	Pleural effusion with positive cytology
	IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

gram, it needs to be clarified whether performing exploratory laparoscopy and assessing non-resective disease during it could be treated similarly.

2. Neoadjuvant chemotherapy — chemotherapy administered in order to make the disease fully operable, e.g. debulking of the tumour and limiting its extension. The Program does not define the number of neoadjuvant chemotherapy cycles, after which the patient should undergo cytoreductive surgery, but this option was only considered as possible. In light of clinical data, it seems that 3–4 cycles of combined chemotherapy with paclitaxel and carboplatin are justified; however, according to the Program other options are also possible [2, 3].
3. Adjuvant chemotherapy — chemotherapy administered after cytoreductive surgery in order to destroy remaining cancer cells.
4. Progression of advanced ovarian cancer — radiological (computed tomography — CT, magnetic resonance imaging — MRI, positron emission tomography — PET, or ultrasonography — US) or clinical (medical history or gynaecological or physical evaluation) signs and symptoms indicating cancer enlargement. Increased levels of serum markers (e.g., CA125, HE4, CEA) unnecessarily have to indicate virtual disease progression and require confirmation by either imaging or clinical feature.

Evaluation of ovarian cancer clinical stage

Bevacizumab treatment is dedicated to patients with stage III and IV OC. Table 2 presents the OC qualification system, effective since 2014, based on a system proposed by FIGO (*Fédération Internationale de Gynécologie et d'Obstétrique*) [9]. The stages potentially qualifying to the Program are shown in blue.

The stage of OC according to FIGO classification is assessed after cytoreductive or laparoscopic operation, based on intraoperative findings, and verified by

histological evaluation. The only exception is stage IV, which needs to be confirmed as follows:

— histological verification [laparoscopy, core-needle biopsy (CNB), excision] of OC from any disease location. If this is impossible, cytological verification alone is acceptable, but it should be supplemented by assessment of biomarkers CA125/CEA ratio > 25 or negative results of GI tract endoscopy. It is connected to the possibility of GI or pancreatic adenocarcinoma dissemination, imitating advanced OC;
— confirming by imaging tests (preferred CT, MRI, and PET) unambiguously metastatic changes or histological verification sites outside peritoneal cavity (e.g. pleural effusion, inguinal, axillary, supraclavicular lymph nodes etc.).

Stage IV should not be diagnosed exclusively based on bilateral pleural effusion; such cases require cytological examination of pleural fluid in order to confirm the presence of OC cells. In patients with non-oncological changes, ineligible to surgery, the clinical stage should be assessed as described above.

Surgical protocol for advanced ovarian cancer

The surgical protocol recommended by the Polish Society of Gynaecological Oncology is available on the website www.ptgo.pl (Fig. 1). Its main part, independent of format, should be a description of the localisation and size of residual cancer tissue. Unfortunately, this is a protocol element commonly ignored by gynaecologists, which makes qualification to the Program impossible. This information also enables a proper therapeutic decision to be made during further steps of therapy.

Patients eligible to the Program — surgical criteria

1. Patients with stage III, after exploratory laparotomy or laparoscopy alone with excision of numerous samples.
2. Patients with stage III, after excision of some cancer sites (e.g. omentum, adnexa, etc.) but with residual disease > 1 cm.
3. All patients with stage IV, regardless of whether they underwent surgery or not and independently of the size of residual disease after operation.

Special groups of patients eligible to the Program

1. **Patients operated at the beginning of the therapy**, but in whom, due to disease intensity, only samples were excised, and then adjuvant chemotherapy with bevacizumab was initiated and the next cytoreductive operation was decided. Bevacizumab could be continued in such patients after cytoreductive interval operation, REGARDLESS of its results, e.g. independently of residual disease, even if its size is < 1 cm.
2. **Patients not operated at the beginning of the therapy** due to the inadequate general health state or disease stage, only samples were excised and imaging evaluations confirming stage III, and then induction therapy without bevacizumab was initiated and interval cytoreductive operation was decided. Those patients will be able to continue bevacizumab treatment after interval cytoreductive operation, but ONLY when residual disease is > 1 cm.

In the last group of patients it should be remembered to make an appropriate time period between bevacizumab treatment and scheduled surgery, which should last for four weeks before and four weeks after operation. It is also acceptable to administer one chemotherapy cycle preceding operation and one cycle after operation without bevacizumab. It does not influence the further possibility of using bevacizumab under the Program.

The group of OC patients, which in the current scope of the Program raises the biggest questions regarding Program interpretation:

1. Patients in stage III after laparoscopic operation, aimed to assess disease clinical stage, during which the stage was found, which is connected with poor prognosis regarding optimal cytoreduction, and in whom chemotherapy was introduced. Currently this diagnostic model is the most advanced procedure of qualification to cytoreductive operation; during this the samples are taken for histological evaluation and to assess the resectability [7, 8].
2. Patients in stage III, after no cytoreductive operation, for example due to general health state or no consent, and diagnosis and stage is assessed as previously described for patients in stage IV. In the ICON7 study those patients were included to the high-risk group and had the greatest benefit from bevacizumab therapy. The Program does not consider this group of patients, which seems not to be justified.

OC patients ineligible to the Program — surgical criteria

1. OC patients with disease verified during laparoscopy or biopsy, clinically and radiologically limited to peritoneal cavity (possible stage II or III), having undergone neoadjuvant chemotherapy, and in whom

PROTOCOL OF OVARIAN CANCER OPERATION version 1. 2015

Patient's name and surname: . . . . . **PESEL:** ☐☐☐☐☐☐☐☐☐☐☐

Diagnosis: . . . . . .

Type of operation:

❑ Primary operation ❑ Interval operation ❑ Secondary operation (treatment of recurrence, non-cured cancer) ❑ Others ❑ Laparoscopy ❑ Laparotomy

Duration of the operation (min.) . . . . . **Operation's description** Date: . . . . . Operator: . . . . . 1 Assist: . . . . . 2 Assist: . . . . . .

Operation's description . . . . . .

LOCALISATION OF CANCER LESIONS BEFORE OPERATION	**SIZE OF RESIDUAL LESIONS** (the greatest size in cm, if > 0)
Fluid: . . . . . ml	
PELVIS:	
❑ Right adnexa	. . . . . cm
❑ Left adnexa	. . . . . cm
❑ Uterus	. . . . . cm
❑ Sigmoid colon and rectum	. . . . . cm
❑ Pouch of Douglas	. . . . . cm
❑ Vesico-uterine pouch	. . . . . cm
❑ Parietal peritoneum	. . . . . cm
❑ Others	
MESOGASTRIC:	
LARGE BOWEL:	
❑ Ascending colon	. . . . . cm
❑ Transverse colon	. . . . . cm
❑ Descending colon	. . . . . cm
❑ Mesentery surface	. . . . . cm
❑ Mesentery root	. . . . . cm
SMALL BOWEL:	
❑ Intestinal loops	. . . . . cm
❑ Mesentery surface	. . . . . cm
❑ Mesentery root	. . . . . cm
GREATER OMENTUM:	
❑ Subcolon	. . . . . cm
❑ Gastrocolic ligament	. . . . . cm
❑ Gastrosplenic ligament	. . . . . cm
PERITONEUM:	
❑ Left upper quadrant of abdomen	. . . . . cm
❑ Right upper quadrant of abdomen	. . . . . cm
EPIGASTRIC:	
❑ Peritoneum of diaphragm's copula	. . . . . cm
❑ Left ❑ Right	. . . . . cm
❑ Glisson's capsule/liver	. . . . . cm
❑ Spleen	. . . . . cm
❑ Hepatic hilus/gall bladder	. . . . . cm
❑ Lesser omentum/stomach/duodenum	. . . . . cm
❑ Others	. . . . . cm
LYMPH NODES:	
❑ Pelvic	. . . . . cm
❑ Periaortic	. . . . . cm
❑ Others	. . . . . cm

LOCALISATION OF CANCER LESIONS BEFORE OPERATION	**SIZE OF RESIDUAL LESIONS** (the greatest size in cm, if > 0)
Fluid: . . . . . ml	
PELVIS:	
❑ Right adnexa	. . . . . cm
❑ Left adnexa	. . . . . cm
❑ Uterus	. . . . . cm
❑ Sigmoid colon and rectum	. . . . . cm
❑ Pouch of Douglas	. . . . . cm
❑ Vesico-uterine pouch	. . . . . cm
❑ Parietal peritoneum	. . . . . cm
❑ Others	
MESOGASTRIC:	
LARGE BOWEL:	
❑ Ascending colon	. . . . . cm
❑ Transverse colon	. . . . . cm
❑ Descending colon	. . . . . cm
❑ Mesentery surface	. . . . . cm
❑ Mesentery root	. . . . . cm
SMALL BOWEL:	
❑ Intestinal loops	. . . . . cm
❑ Mesentery surface	. . . . . cm
❑ Mesentery root	. . . . . cm
GREATER OMENTUM:	
❑ Subcolon	. . . . . cm
❑ Gastrocolic ligament	. . . . . cm
❑ Gastrosplenic ligament	. . . . . cm
PERITONEUM:	
❑ Left upper quadrant of abdomen	. . . . . cm
❑ Right upper quadrant of abdomen	. . . . . cm
EPIGASTRIC:	
❑ Peritoneum of diaphragm's copula	. . . . . cm
❑ Left ❑ Right	. . . . . cm
❑ Glisson's capsule/liver	. . . . . cm
❑ Spleen	. . . . . cm
❑ Hepatic hilus/gall bladder	. . . . . cm
❑ Lesser omentum/stomach/duodenum	. . . . . cm
❑ Others	. . . . . cm
LYMPH NODES:	
❑ Pelvic	. . . . . cm
❑ Periaortic	. . . . . cm
❑ Others	. . . . . cm

Intraoperative staging according FIGO 2014 classification . . . . . **Maximal size of gross residual disease after cytoreduction** . . . . . cm

Intraperitoneal catheter: YES ❑ NO ❑ **Results of intraoperative assessment** . . . . . .

Name and stamp of the centre

Stamp and signature of physician

POLSKIE TOWARZYSTWO GINEKOLOGII ONKOLOGICZNEJ, ul. Promyka 13, 01-604 Warszawa
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Translation: dr n. med. Dariusz Stencel

Figure 1. Polish Society of Gynaecological Oncology. Protocol of ovarian cancer operation. Version 1.2015

during interval cytoreductive operation optimal or complete cytoreduction was achieved (residual disease < 1 cm).
2. Patients who have undergone primary cytoreduction, in whom, during operation, disease limited to the pelvis was revealed (FIGO I/II), regardless of cytoreduction extension.
3. Patients with advanced OC, who underwent initial surgery, with residual disease < 1 cm.

Time limits according to inclusion of OC patients to the Program

According to the criteria, patients could be qualified to the Program:
— from the first chemotherapy cycle or the second cycle, but only if chemotherapy was initiated less than four weeks after cytoreductive operation;
— no earlier than 28 days after surgery;
— after CT of abdominal cavity and pelvis, which should be performed no earlier than four weeks after operation, but no later than two weeks after initiating of chemotherapy.

The above mentioned three conditions practically mean that:
— in patients in stage IV, who were not operated, bevacizumab treatment is initiated from the first cycle. Before first chemotherapy cycle with bevacizumab CT should be taken (Fig. 2);
— in patients in stage III/IV, after cytoreductive operation, CT must be performed four weeks after operation at the earliest; after this, bevacizumab treatment could be initiated. However, literature data suggest that postoperative chemotherapy should be initiated up to four weeks after operation [10]. Thereby, one chemotherapy cycle without bevacizumab is recommended, **and then at least four weeks after operation, but no later than two weeks later the first chemotherapy cycle CT should be performed**, and bevacizumab should be added after the second chemotherapy cycle. In such cases the "time window" to perform CT lasts only 1–14 days, depending on the time of administration of the first chemotherapy cycle (Fig. 3).

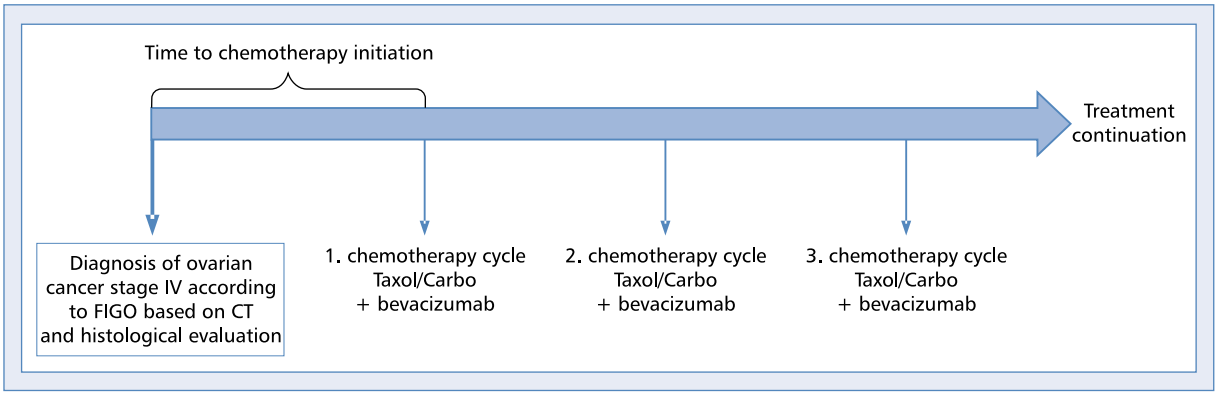

Figure 2. Timely criteria of inclusion to the Program for patients with ovarian cancer stage IV according FIGO classification, not treated surgically

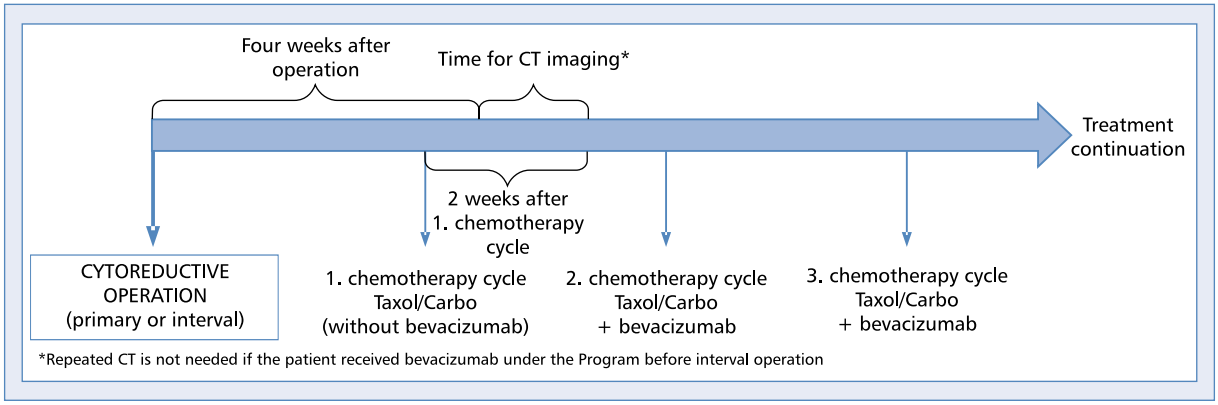

Figure 3. Timely criteria of inclusion to the Program for patients with ovarian cancer stage III/IV according FIGO classification after cytoreductive operation (primary or interval)

Summary

According to unpublished data of Bodnar et al., approximately 80% of ovarian cancer patients in Poland are operated on in over 200 departments. In other words, many departments treat surgically less than 10 cases per year. Taking into account the complexity of cytoreductive operations in OC patients, it could be assumed that the percentage of optimal cytoreduction in those patients could be even less than presented above (see — the Introduction). Obviously, a significant — difficult to precisely assess — portion of patients would not qualify to the Program due to their general health state; however, it seems that a markedly higher number of OC patients could be, or even should be qualified to the MoH Program "Treatment of patients with advanced ovarian cancer". Unfortunately, there are many patients in clinical practice with inadequately stated surgical reports, with inappropriate time windows, essential to qualify patients to the Program, not being informed about Polish clinical sites using the treatment of OC under the Program, and as a result, deprived of an opportunity to improve survival. Obviously, this situation demands changes, which should be initiated immediately: educational actions leading to improved medical documentation, knowledge about the Program criteria, timelines, as well as a list of centres having the possibility to use bevacizumab in OC patients (Tab. 3). It is also essential to adjust the Program rules to new evidence and development of OC treatment techniques, which in recent years significantly changed, making some parts of the Program no longer current. Up-to-date recommendations of scientific societies and cooperation with public payers and drug manufacturers are also indicated.

Table 3. List of centres carrying out the Drug Program of Ministry of Health "Treatment of patients with advanced ovarian cancer". State as of 1 December 2016

National Health Fund — regional branch	Healthcare provider	City	Address
Dolnośląski	4 Wojskowy Szpital Kliniczny z Polikliniką, Samodzielny Publiczny Zakład Opieki Zdrowotnej, Wrocław	Wrocław	Rudolfa Weigla 5
	Dolnośląskie Centrum Onkologii, Wrocław	Wrocław	Hirszfelda 12
	Specjalistyczny Szpital im. Dra Alfreda Sokołowskiego	Wałbrzych	Alfreda Sokołowskiego 4
	Miedziowe Centrum Zdrowia S.A., Lubin	Lubin	Marii Skłodowskiej-Curie 66
	Wielospecjalistyczny Szpital — Samodzielny Publiczny Zespół Opieki Zdrowotnej, Zgorzelec	Zgorzelec	Lubańska 11–12
	Wojewódzkie Centrum Szpitalne Kotliny Jeleniogórskiej	Jelenia Góra	Michała Kleofasa Ogińskiego 6
	Wojewódzki Szpital Specjalistyczny, Wrocław	Wrocław	Kamieńskiego 73a
	Samodzielny Publiczny Zespół Opieki Zdrowotnej, Świdnica	Świdnica	Leśna 27–29
Kujawsko-Pomorski	Wojewódzki Szpital Zespolony im. L. Rydygiera, Toruń	Toruń	Św. Józefa 53–59
	Centrum Onkologii im. Prof. Franciszka Łukaszczyka, Bydgoszcz	Bydgoszcz	I. Romanowskiej 2
Lubelski	Centrum Onkologii Ziemi Lubelskiej im. Św. Jana z Dukli	Lublin	Dr. K. Jaczewskiego 7
	Samodzielny Publiczny Szpital Wojewódzki im. Papieża Jana Pawła II, Zamość	Zamość	Aleje Jana Pawła II 10
	Samodzielny Publiczny Szpital Kliniczny Nr 1, Lublin	Lublin	Staszica 16
Lubuski	Wielospecjalistyczny Szpital Wojewódzki, Gorzów Wlkp. Spółka z ograniczoną odpowiedzialnością	Gorzów Wielkopolski	Jana Dekerta 1
	Wojewódzki Szpital Kliniczny im. Karola Marcinkowskiego, Zielona Góra Spółka z ograniczoną odpowiedzialnością	Zielona Góra	Zyty 26
Łódzki	Wojewódzki Specjalistyczny Szpital im. M. Pirogowa, Łódź	Łódź	Wólczańska 191/195
	Wojewódzki Szpital Specjalistyczny im. M. Kopernika, Łódź	Łódź	Pabianicka 62

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Table 3 (cont.). List of centres carrying out the Drug Program of Ministry of Health "Treatment of patients with advanced ovarian cancer". State as of 1 December 2016

National Health Fund — regional branch	Healthcare provider	City	Address
Małopolski	Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie	Kraków	Garncarska 11
	Szpital Specjalistyczny im. Jędrzeja Śniadeckiego, Nowy Sącz	Nowy Sącz	Młyńska 10
	Samodzielny Publiczny Zakład Opieki Zdrowotnej, Szpital Uniwersytecki, Kraków	Kraków	Kopernika 36
	Szpital Specjalistyczny im. Ludwika Rydygiera, Kraków Spółka z ograniczoną odpowiedzialnością	Kraków	Os. Złotej Jesieni 1
	Szpital Wojewódzki im. Św. Łukasza, Samodzielny Publiczny Zakład Opieki Zdrowotnej, Tarnów	Tarnów	Lwowska 178a
Mazowiecki	Wojskowy Instytut Medyczny	Warszawa	Szaserów 128
	Wojewódzki Szpital Zespolony, Płock	Płock	Medyczna 19
	Mazowiecki Szpital Bródnowski, Warszawa Sp. z o.o.	Warszawa	Kondratowicza 8
	Mazowiecki Szpital Specjalistyczny Spółka z ograniczoną odpowiedzialnością	Radom	Juliana Aleksandrowicza 5
	Mazowiecki Szpital Wojewódzki, Siedlce Sp. z o.o.	Siedlce	Poniatowskiego 26
	Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie	Warszawa	Wawelska 15b
	Magodent Spółka z ograniczoną odpowiedzialnością	Warszawa	Gen. A.E. Fieldorfa „Nila" 40
	Centralny Szpital Kliniczny MSWiA, Warszawa	Warszawa	Wołoska 137
	Krajowa Fundacja Medyczna	Warszawa	Łabiszyńska 25
	Europejskie Centrum Zdrowia Otwock Sp. z o.o.	Warszawa	Żytnia 16/C
	Szpital Kliniczny im. Ks. Anny Mazowieckiej	Warszawa	Karowa 2
Opolski	Samodzielny Publiczny Zakład Opieki Zdrowotnej — Opolskie Centrum Onkologii im. Prof. T. Koszarowskiego	Opole	Katowicka 66a
Podkarpacki	Mrukmed Lekarz Beata Madej-Mruk I Partner, Spółka Partnerska	Rzeszów	Partyzantów 30a
	Szpital Specjalistyczny, Brzozów, Podkarpacki Ośrodek Onkologiczny im. Ks. B. Markiewicza	Brzozów	Ks. Józefa Bielawskiego 18
	Kliniczny Szpital Wojewódzki Nr 1 im. Fryderyka Chopina, Rzeszów	Rzeszów	Fryderyka Szopena 2
	Wojewódzki Szpital im. Zofii z Zamoyskich Tarnowskiej, Tarnobrzeg	Tarnobrzeg	Szpitalna 1
Podlaski	Białostockie Centrum Onkologii im. Marii Skłodowskiej-Curie	Białystok	Ogrodowa 12
	Uniwersytecki Szpital Kliniczny, Białystok	Białystok	M.C. Skłodowskiej 24 A
Pomorski	Uniwersyteckie Centrum Kliniczne	Gdańsk	Dębinki 7
	Szpitale Wojewódzkie, Gdynia Spółka z ograniczoną odpowiedzialnością	Gdynia	Powstania Styczniowego 1
	Szpital Specjalistyczny, Słupsk	Słupsk	Prof. Lotha 26
	Szpital im. Mikołaja Kopernika	Gdańsk	Nowe Ogrody 1–6

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Table 3 (cont.). List of centres carrying out the Drug Program of Ministry of Health "Treatment of patients with advanced ovarian cancer". State as of 1 December 2016

National Health Fund — regional branch	Healthcare provider	City	Address
Śląski	SPZOZ Wojewódzki Szpital Specjalistyczny Nr 4, Bytom	Bytom	Aleja Legionów 10
	Centrum Medyczne „Małgorzata" Spółka z ograniczoną odpowiedzialnością	Częstochowa	Warszawska 30
	Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie	Gliwice	Wybrzeże Armii Krajowej 15
	Samodzielny Publiczny Zakład Opieki Zdrowotnej Wojewódzki Szpital Specjalistyczny Nr 3, Rybnik	Rybnik	Energetyków 46
	Beskidzkie Centrum Onkologii — Szpital Miejski im. Jana Pawła II, Bielsko-Biała	Bielsko-Biała	Wyzwolenia 18
	Samodzielny Publiczny Szpital Kliniczny im. Andrzeja Mielęckiego Śląskiego Uniwersytetu Medycznego, Katowice	Katowice	Francuska 20/24
	Katowickie Centrum Onkologii	Katowice	Raciborska 26
	SP Szpital Kliniczny Nr 7 Śląskiego Uniwersytetu Medycznego, Katowice, Górnośląskie Centrum Medyczne im. Prof. Leszka Gieca	Katowice	Ziołowa 45–47
	Wojewódzki Szpital Specjalistyczny im. N.M.P.	Częstochowa	Bialska 104/118
Świętokrzyski	Świętokrzyskie Centrum Onkologii, Samodzielny Publiczny Zakład Opieki Zdrowotnej, Kielce	Kielce	Artwińskiego 3
Warmińsko-Mazurski	Wojewódzki Szpital Zespolony, Elbląg	Elbląg	Królewiecka 146
	Wojewódzki Szpital Specjalistyczny, Olsztyn	Olsztyn	Żołnierska 18
	Samodzielny Publiczny Zakład Opieki Zdrowotnej Ministerstwa Spraw Wewnętrznych i Administracji z Warmińsko-Mazurskim Centrum Onkologii, Olsztyn	Olsztyn	Wojska Polskiego 37
Wielkopolski	Pleszewskie Centrum Medyczne, Pleszew Sp. z o.o.	Pleszew	Poznańska 125a
	Szpital Kliniczny Przemienienia Pańskiego Uniwersytetu Medycznego im. Karola Marcinkowskiego, Poznań	Poznań-Stare Miasto	Długa 1/2
	Wielkopolskie Centrum Onkologii im. Marii Skłodowskiej-Curie	Poznań-Stare Miasto	Garbary 15
	Wojewódzki Szpital Zespolony, Konin	Konin	Szpitalna 45
	Ginekologiczno-Położniczy Szpital Kliniczny Uniwersytetu Medycznego im. Karola Marcinkowskiego, Poznań	Poznań-Jeżyce	Polna 33
Zachodniopomorski	Samodzielny Publiczny Szpital Kliniczny Nr 2 Pomorskiego Uniwersytetu Medycznego	Szczecin	Powstańców Wielkopolskich 72
	Zachodniopomorskie Centrum Onkologii	Szczecin	Strzałowska 22
	Szpital Wojewódzki im. M. Kopernika, Koszalin	Koszalin	Chałubińskiego 7

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