Bevacizumab for advanced ovarian cancer treatment. A GRADE based approach

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ABSTRACT

BACKGROUND: in advanced ovarian cancer, over the last 10 years no studies have demonstrated more appropriate therapeutic options compared to the current standard Carboplatin-Paclitaxel (Cb-P) regimen. Two phase III randomized studies (GOG-218 and ICON-7) have recently demonstrated the efficacy of bevacizumab (recombinant monoclonal antibody that binds with a high affinity to VEGF-A) in adjunct to Cb-P, with 12-15 months maintenance treatment.

METHODS: the quality of evidence provided was assessed by the use of the GRADE method. Each outcome (deemed to be essential for the purpose of evaluation of the intervention) was assessed to express the degree of confidence in the entity of the beneficial and/or harmful effects of the intervention. Thus, limitations in the quality of conducting the studies (risk of bias), direct applicability/relevance of results to the target population, and precision of results were taken into account.

RESULTS: the GOG-218 and the ICON7 study (high-risk subgroup) demonstrated with MODERATE confidence an improvement in critical outcomes PFS and OS, with an absolute reduction of 96 (GOG-218) – 103 (ICON-7) episodes of progression, and 40 (GOG-218) – 135 (ICON-7) deaths per 1 000 patients. A marked increase in risk of hypertension of Grade ≥3 was observed, with an absolute increase of 59 episodes per 1 000 patients in the ICON-7 study, and 157 episodes in the GOG-218 study, respectively, the majority of which were controlled by means of appropriate treatment. The increased risk of other adverse events considered was negligible.

CONCLUSIONS: the positive effects produced should be viewed as taking prevalence over the negative effects (FAVOURABLE benefit/harm ratio).

Key words: Ovarian cancer; Bevacizumab; Quality of evidence; GRADE system

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OVARIAN CANCER: EXTENT OF THE PROBLEM

Risk factors

Ovarian cancer causes more deaths than any other cancer of the female reproductive system, but it accounts for only about 3% of all cancers in women [1].

Epithelial forms have an incidence of 60%

representing 30% of cancers of the female reproductive system [1, 2].

Forty to sixty per cent of germinal ovarian cancers are diagnosed in women below the age of 20 years; conversely, epithelial cancers affect both women of reproductive age and the elderly [3].

Scientific findings have led to the identification of three classes of risk factors: hormonal, environmental and familial. The main risk factors in superficial epithelial-stromal forms are linked to hormonal balance, in particular ovulation: indeed, recently, an increased risk has been registered in menopausal women on replacement hormone therapy (oestrogens) for at least 10 years [4]. On the contrary, a high number of pregnancies carried to term and the use of oral contraceptives constitute a protective factor [4, 5]. However, even in the presence of these associations, no evidence demonstrating a direct link between the above risk factors and the process of carcinogenesis is currently available [5, 6].

The majority of epithelial ovarian cancers are of a sporadic origin, although a familial or hereditary pattern is observed in 5-10% of cases. Biomolecular risk factors are represented by mutations to the BRCA-1 and BRCA-2 genes. A mutation in the BRCA-1 gene is found in 5% of patients with an onset of cancer by the age of 70 years, with an overall risk of a combined mutation of BRCA-1 and BRCA-2 by the same age ranging from 20 to 60% [7, 8].

A correlation with asbestos and talc, alcohol abuse, obesity and a fat-rich diet has been described [9]. However, no evident associations have been detected for smoking [10] and caffeine [11].

Incidence

In Italy 4 900 estimated diagnoses were formulated in 2012, representing almost 3% of all cancers diagnosed in women. An estimated lifetime incidence of 1 in 75 women will develop ovarian cancer [12].

The incidence of ovarian cancer has displayed a modest reduction since the mid-1990s, taking into account the effect produced by progressive ageing of the population [13]. This type of cancer presents a North-South gradient: 12.1 cases every 100 000 women/year in the North, 10.1 in Central Italy, and 9.7 in the South have been diagnosed, respectively [14].

In line with current rates of incidence, in view of the progressive ageing of the population, approximately 5 400 new cases in 2020, and approximately 5 900 in 2030 can be estimated [15].

Mortality

Ovarian cancer has been listed as one of the first 5 causes of death from cancer among women in the 50-69 year age group (7% of total number of deaths) [16]. Mortality rates have featured a somewhat constant trend over time [13]. Mortality caused by this form of cancer likewise presents a North-South gradient: 7 deaths per 100 000 women/year in the North, 6.1 in the Centre, and 5.2 in the South are reported, respectively [17].

Survival

The aggressive nature and frequently late diagnosis of these forms of cancer strongly influences prognosis: 41% of women who developed ovarian cancer between the years 2000-2005, are still alive 5 years after diagnosis (72% at 1 year and 50% at 3 years). Compared to the previous five-yearly periods, survival rates have improved slightly, with an increase of 3% compared to women who developed the disease in the first half of the 1990s [18]. As the disease is correlated with a clinical picture that is frequently fatal in the short-term, it is not surprising to observe how, subsequent to diagnosis, the rate of survival at 5 years is markedly increased in the medium-long term (50% after 1 year, 80% after 5 years) [19]. Moreover, no prognostic gradients by geographic area are observed: slight differences on the threshold of statistical significance are however observed between central Italy (41% at 5 years) and Southern Italy (35%) [20].

Prevalence

A total of 37 826 women with a previous history of ovarian cancer are resident in Italy, representing 2.5% of all cancer patients [21]. More than 60% of prevalent cases were diagnosed at least 5 years ago. A higher percentage of prevalent cases is observed in the 60-74 year age group (310/100 000). Similar values are

reported for Central-Northern areas (149, 133 and 142/100 000 the proportions observed in the NW, NE and Centre, respectively), whilst lower rates are reported for Southern Italy (98/100 000) [22]. Similar to findings reported with regard to rates of incidence, mortality and survival, prevalence rates have also displayed a basically stable trend. The ovaries currently represent the ninth most common site of cancer in order of prevalence [21, 22].

OVARIAN CANCER: THERAPEUTIC APPROACH

The standard system of classification used in staging ovarian epithelial cancers is that of the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) [23], with disease staging based on the performing of a primary surgical intervention according to a clearly defined timeline established by the guidelines published by the EORTC Gynaecological Cancer Group. Consequently, surgery is viewed as an integral part of both diagnosis and correct staging of the disease.

In patients affected by early ovarian cancer in which manifestation of the disease is limited to the pelvic area (FIGO I-IIA), radical surgery is effective in 70% of cases. In these stages of the disease, surgery comprises a bilateral hysterectomy and oophorosalpingectomy, infracolic omentectomy, peritoneal washing and biopsies, in addition to exploration of the retroperitoneal space and the pelvic and para-aortic areas. Despite the radical nature of surgery, these stages feature a 30% risk of relapse, thus implying the need for adjuvant chemotherapy.

With the aim of identifying patients better suited to benefitting from medical treatment, this clinical subset has been divided into three risk categories (high-intermediate-low risk of relapse) thanks to the identification of independent prognostic factors such as: degree of differentiation, FIGO stage, substage (in the case of pre-surgery rupture of the ovarian capsule), age, histological subtype (poorer prognosis in the undifferentiated or clear cell types) and presence of ascites [24].

In low risk patients (FIGO stages IA and IB with a clearly differentiated disease and histotype other than clear cell carcinoma), surgery is decisive in 95% of cases, with no evidence supporting the advantage of subsequent adjuvant chemotherapy.

Intermediate (FIGO stage IA-IB, moderately differentiated) and high risk cancer patients (FIGO stage IC-II, poorly differentiated or clear cell) present a risk of relapse ranging from 25 to 40%, and adjuvant chemotherapy is indicated. To date, standard treatment is represented by the use of 4-6 cycles of carboplatin as a *single agent* or 3-6 cycles of a combination of carboplatin and paclitaxel (Cb-P) [24, 25].

In advanced stage ovarian cancer (FIGO stages III and IV) surgery is performed to remove all visible traces of neoplasia (cytoreduction or debulking surgery), as well as to assess extension of the disease, particularly as the presence of post-surgical tumour residues is considered an independent prognostic factor, which is closely linked to survival [26]. Indeed, patients who have undergone optimal cytoreduction (with absence of macroscopic tumour residues), present a markedly decreased risk of relapse. In inoperable advanced stage cancers, secondary surgery (interval surgery) should be considered subsequent to neo-adjuvant chemotherapy (3 cycles), with this therapeutic option displaying no substantial differences compared to the standard approach (surgery followed by chemotherapy) in terms of progression-free survival and overall survival [27, 28].

Currently, the standard adjuvant or first-line treatment in ovarian cancer is represented by the Cb-P combination [29-32], although this line of treatment may hopefully be replaced, particularly in view of the disappointing results obtained in the long-term follow-up of registrational studies demonstrating rates of relapse ranging between 70-80% over the first 2 years.

A series of studies has investigated alternative standards aimed at replacing conventional treatment regimens. The strategies adopted included the addition of a third drug (GOG-182-ICON-5 study, substantially negative), the use of new combinations (MITO-2 study displaying efficacy of pegylated liposomal carboplatin and doxorubicin compared with standard treatment), alteration in the *timing* of treatment (evidence of an improved tolerability of the weekly schedule) [33] or the means of administration (greater efficacy of intraperitoneal CT in the GOG-172 study [34] although with marked toxicity that limits its use in current clinical practice [35]).

Over the last 10 years no studies have

therefore demonstrated more appropriate therapeutic options compared to the current standard regimen, although promising prospective have been provided by the use of anti-angiogenic drugs.

Two phase III randomized studies (GOG-218 [36] and ICON-7 [37]) have recently demonstrated the efficacy of bevacizumab (recombinant monoclonal antibody that binds with a high affinity to VEGF-A) in adjunct to Cb-P, with 12-15 months maintenance treatment.

The EMA SCP of December 2011 stated that: *"Avastin, in combination with carboplatin and paclitaxel is indicated in the first-line treatment of epithelial ovarian cancer, of the Fallopian tubes cancer, or advanced stage primary peritoneal carcinoma (FIGO stage IIIB, IIIC and IV).*

Avastin is administered in combination with carboplatin and paclitaxel for a total of up to 6 cycles of treatment, followed by administration of Avastin as a single agent until disease progresses, or for a maximum of 15 months, or until unacceptable toxicity is manifested, whichever occurs earlier. The recommended dose of Avastin is 15mg/kg body weight, to be administered once every 3 weeks by intravenous infusion" [38].

BEVACIZUMAB + CB-P: QUALITY OF EVIDENCE PROVIDED AND HARM/ BENEFIT RATIO

In order to assess the quality of evidence provided it is possible to adopt the approach used by Working Groups for guidelines development. The valid and accurate classification of the quality of findings may contribute towards preventing errors in the interpretation of data. An explicit system of classification ranging from "high" to "very low" – may therefore be of importance for the purpose of the validation and reproducibility of the process of evaluation and formulation of potential recommendations. Although the quality of proof provided constitutes a continuum, and therefore each classification will inevitably result in a simplification, the GRADE method possesses the undeniable advantage of simplicity and transparency [39].

Using the GRADE method the quality of evidence is operationally defined as the judgement that allows one to ascertain up to what point the benefit/harm ratio can be reliably adopted in favour of/against the recommendation of the use of a specific strategy [40].

The clinical question should be explicitly defined taking into account the dimensions represented by the PICO acronym, indicating the need to define:

a) The target Population towards which the recommendation is directed;
b) Means of Intervention (drug, surgery or rehabilitation, etc) implicated in the recommendation;
c) Comparison (other drug, placebo, …), or what other form of intervention/ strategy should be considered in the recommendation;
d) Outcome relating to the formulation of the recommendation.

Each outcome (deemed to be essential for the purpose of evaluation of the intervention) is assessed according to a systematic, explicit grading of quality (High, Moderate, Low, Very Low), to express the degree of confidence in the entity of the beneficial and/or harmful effects of the intervention [41] (Table 1).

Using the GRADE method assessment of the quality of evidence should not only be based on the appropriateness of design of each single study available (randomized study, observational study, other type of study design), but should also take into account other factors relating to:

a) limitations in the quality of conducting the studies (risk of bias);
b) direct applicability/relevance of results to the target population;
c) precision of results.

Subsequent to grading of quality for each single outcome, an overall judgement of quality should be formulated. The method indicates the following line of behaviour:

a) if the results progress in opposite directions (e.g. the treatment investigated is better in terms of efficacy, but poorer with regard to adverse effects), overall quality is attributed on the basis of the worst evaluation provided, i.e. taking the outcome receiving the lowest quality evaluation as being the most representative;
b) if the results progress in the same direction for all outcomes (benefits or harm), overall quality is based on the

TABLE 1

GRADE METHOD: GRADING OF QUALITY OF THE EVIDENCE		
LEVEL OF QUALITY	SIGNIFICANCE	CONSEQUENCE
HIGH	High degree of confidence in results	It is highly unlikely that further studies will alter confidence in estimation of the effect
MODERATE	Discreet degree of confidence in results	It is likely that further studies may confirm or alter confidence in estimation of the effect
LOW	The results are scarcely plausible	Further studies should be undertaken to obtain reliable estimations of the positive and negative effects of the intervention
VERY LOW	The data examined are completely unreliable	No confidence may be placed in the available estimation of the effects

quality attributed to a single essential outcome, which alone would suffice for the purpose of formulation of the recommendation.

A decision in favour of or against use of the treatment should be based on the balance reached between positive (benefits) and negative (harmful) effects of the intervention. In principle, if the positive effects prevail over the negative effects, the recommendation should be in favour of the intervention, whilst vice versa it should be opposed to the recommendation.

The balance between positive and negative effects should take into account the number and weight of each single factor. The weight of each positive or negative effect is moreover influenced by the importance of the outcome and by the clinical and epidemiological relevance (magnitude of the relative and absolute effect).

Bevacizumab in the treatment of advanced stage ovarian cancer: definition of the question

The SPC of the EMA "influences" (in terms of applicability) the formulation of the question: "Efficacy of Bevacizumab as an adjunct to conventional CT in the first-line treatment of advanced stage ovarian cancer", which in PICO terms is structured as follows:

P Patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer;
I Bevacizumab 15mg/Kg every 3 weeks up to progression of disease, or for a maximum of 15 months, as an adjunct to the Cb-P combination;
C Cb-P;
O *benefit*: PFS, OS;
harm: worsening of Quality of Life (QoL), hypertension G≥3, perforation of G.I. tract, thromboembolic event G≥3, bleeding G≥3.

Bevacizumab in the treatment of advanced stage ovarian cancer: evidence available

The GOG-218 study [36] fully meets the requirement of the question in terms of target population and therapeutic strategy. Conversely, the ICON-7 study [37] also comprised patients at an earlier stage ("high risk" stage I and IIA, stage III with residues <1cm), bevacizumab was administered at a lower dose (7.5mg/Kg every 3 weeks), and was limited to a maximum of 12 months. It however proved possible to extrapolate (by means of pre-planned analysis) a sub-population (using factors defined by stratification) of characteristics to some extent similar to those of the GOG-218 study.

Bevacizumab in the treatment of advanced stage ovarian cancer: assessment of evidence of a beneficial outcome (Tables 2-4)

a) Progression-free Survival (PFS)
   I. The primary endpoint in both studies considered was PFS. The adequacy of this endpoint in assessing the efficacy of therapeutic strategies in ovarian cancer is widely acknowledged [42-45], particularly in the presence of a duration of Survival Post Progression (SPP) [46] exceeding 12 months (29 months in the GOG-218 study), and naturally in the presence of a crossover from the control arm to the experimental arm (39% in the GOG-218 study) [47].
   II. The GOG-218 study provides HIGH quality evidence of a relative decrease of 33% in the risk of disease progression, with an absolute benefit corresponding to a decrease of 96 episodes of progression per 1 000 cases.
   III. Intention to treat (ITT) analysis of the relative efficacy of bevacizumab in the ICON-7 study is biased by the nonproportional hazards, an essential assumption in calculation of the hazard ratio (HR). Calculation of the differences between the areas under the PFS curves (restricted mean survival time [48]) however reveals an advantage of 1.7 months for the experimental arm. A LOW quality is yielded, in view of the imprecise nature of the estimation and to the fact that the finding is not immediately transferable to the target population.
   PFS analysis in the high-risk sub-population highlights, with a MODERATE quality (risk of bias in subgroup analysis), a 27% relative decrease in the risk of progression, with an absolute benefit corresponding to a decrease of 103 episodes of progression per 1 000 cases. A difference of 3.6 months was observed between the median PFS in this subgroup of patients.
b) Overall Survival (OS)
   I. The GOG-218 study highlights, with a MODERATE quality (due to crossover = 39%), a 12% relative decrease in mortality rate, with an absolute benefit corresponding to a decrease of 40 deaths per 1 000 cases.
   II. ITT analysis of the ICON-7 study highlights, with a MODERATE quality (due to the lack of immediate transferability to the target population), a 15% relative decrease in risk of mortality, with an absolute benefit corresponding to a decrease of 31 deaths per 1 000 cases.
   Analysis of OS in the high-risk sub-population highlighted, with a MODERATE quality (risk of bias in analysis of subgroups), a 36% relative decrease in risk of mortality, with an absolute benefit corresponding to a decrease of 135 deaths per 1 000 cases. A difference of 7.8 months was observed between the median PFS in this subgroup of patients.

Bevacizumab in the treatment of advanced ovarian cancer: assessment of evidence of a harmful outcome (Tables 2-4)

a) Hypertension Grade ≥3
   I. The GOG-218 study underlined, with a HIGH quality, an absolute increase ranging from 94 to 244 episodes of hypertension (point estimate: 157 events) per 1 000 cases.
   II. The ICON-7 study highlighted, with a HIGH quality, an absolute increase ranging from 2 to 251 episodes of hypertension (point estimate: 59 events) per 1 000 cases.
b) Perforation of the G.I. tract
   I. The GOG-218 study underlines, with a MODERATE quality (due to the low number of events observed), an absolute increase ranging from 1 to 71 episodes of perforation (point estimate: 13 events) per 1 000 cases.
   II. The ICON-7 study highlights, with a MODERATE quality (due to the low number of events observed) an absolute difference ranging from -1 to +45 episodes of perforation (point estimate: 9 events) per 1 000 cases.
c) Thromboembolic events Grade ≥3
   I. The GOG-218 study underlined, with a MODERATE quality (due to the

TABLE 2

GOG-218 STUDY: SUMMARY OF EVIDENCE OBTAINED

Limitations of the Study			Events / Patients		Magnitude of the effect		Quality (GRADE)
Risk of bias	*Indirectness*	*Imprecision*	Bev + CbP	CbP	relative	absolute*	
PROGRESSION-FREE SURVIVAL (PFS)							
no serious limitation	no serious limitation	no serious limitation	360/623	423/625	HR 0.77 (0.68-0.87)	↓96 per 1000 (↓51 - ↓141)	⊕⊕⊕⊕ HIGH
OVERALL SURVIVAL (OS)							
serious[1]	no serious limitation	no serious limitation	269/623	298/625	HR 0.88 (0.75-1.04)	↓40 per 1000 (↓92 - ↓13)	⊕⊕⊕⊙ MODERATE
HYPERTENSION GRADE ≥3							
no serious limitation	no serious limitation	no serious limitation	139/608 (22.9%)	43/601 (7.1%)	RR 3.19 (2.31-4.41)	↓157 per 1000 (↓94 - ↓244)	⊕⊕⊕⊕ HIGH
PERFORATION G.I. TRACT							
no serious limitation	no serious limitation	serious[2]	10/608 (1.6%)	2/601 (0.3%)	RR 4.94 (1.09-22.46)	↓13 per 1000 (↓1 - ↓71)	⊕⊕⊕⊙ MODERATE
THROMBOEMBOLIC EVENT GRADE ≥3							
no serious limitation	no serious limitation	serious[3]	41/608 (6.7%)	35/601 (5.8%)	RR 1.16 (0.75-1.80)	↓9 per 1000 (↓15 - ↓47)	⊕⊕⊕⊙ MODERATE
BLEEDING GRADE ≥3							
no serious limitation	no serious limitation	serious[2,3]	13/608 (2.1%)	5/601 (0.8%)	RR 2.57 (0.92-7.15)	↓13 per 1000 (↓1 -↓51)	⊕⊕⊕⊙ MODERATE

* GRADEpro. Version 3.2 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann, 2008

[1] 39% crossover; [2] few events; [3] wide confidence intervals

TABLE 3

ICON-7 STUDY: SUMMARY OF EVIDENCE OBTAINED

Limitations of the Study			Events / Patients		Magnitude of the effect		Quality (GRADE)
Risk of bias	*Indirectness*	*Imprecision*	Bev + CbP	CbP	relative	absolute*	
PROGRESSION-FREE SURVIVAL (PFS)							
no serious limitation	serious[1]	serious[2]	470/764	464/764	HR 0.87 (0.77-0.99)	↓51 per 1000 (↓4 - ↓94)	⊕⊕⊙⊙ LOW
OVERALL SURVIVAL (OS)							
no serious limitation	serious[1]	no serious limitation	178/764	200/764	HR 0.85 (0.69-1.04)	↓31 per 1000 (↓73 - ↑9)	⊕⊕⊕⊙ MODERATE
HYPERTENSION GRADE ≥3							
no serious limitation	no serious limitation	no serious limitation	46/745 (9.7%)	2/753 (0.3%)	RR 23.25 (5.66-95.42)	↑59 per 1000 (↑2 - ↑251)	⊕⊕⊕⊕ HIGH
PERFORATION G.I. TRACT							
no serious limitation	no serious limitation	serious[3]	10/745 (1.3%)	3/753 (0.4%)	RR 3.37 (0.93-12.19)	↑9 per 1000 (↓1 - ↑45)	⊕⊕⊕⊙ MODERATE
THROMBOEMBOLIC EVENT GRADE ≥3							
no serious limitation	no serious limitation	no serious limitation	32/745 (4.3%)	13/753 (1.7%)	RR 2.49 (1.32-4.70)	↑26 per 1000 (↑6 - ↑64)	⊕⊕⊕⊕ HIGH
BLEEDING GRADE ≥3							
no serious limitation	no serious limitation	serious[3]	2/745 (0.3%)	2/753 (0.3%)	RR 1.01 (0.14-7.16)	0 per 1000 (↓2 - ↑16)	⊕⊕⊕⊙ MODERATE

* GRADEpro. Version 3.2 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann, 2008

[1] 70% population not corresponding (due to stage) to that of the sample examined; [2] non proportional hazards; [3] few events

TABLE 4

ICON-7 STUDY: SUMMARY OF EVIDENCE OBTAINED (PFS AND OS) IN THE "HIGH-RISK" SUB-POPULATION

PROGRESSION-FREE SURVIVAL (PFS)							
Limitations of the Study			Events / Patients		Magnitude of the effect		Quality (GRADE)
Risk of bias	*Indirectness*	*Imprecision*	Bev + CbP	CbP	relative	absolute*	
serious[1]	no serious limitation	no serious limitation	190/231	196/234	HR 0.73 (0.60-0.93)	↓103 per 1000 (↓22 - ↓174)	⊕⊕⊕⊙ MODERATE
OVERALL SURVIVAL (OS)							
Limitations of the Study			Events / Patients		Magnitude of the effect		Quality (GRADE)
Risk of bias	*Indirectness*	*Imprecision*	Bev + CbP	CbP	relative	absolute*	
serious[1]	no serious limitation	no serious limitation	79/231	109/234	HR 0.64 (0.48-0.85)	↓135 per 1000 (↓53 - ↓206)	⊕⊕⊕⊙ MODERATE

* GRADEpro. Version 3.2 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann, 2008
[1] specific non-dimensioning for the subgroup examined

wide confidence intervals observed), an absolute difference that ranged from -15 to +47 thromboembolic events (point estimate: 9 events) per 1 000 cases.

II. The ICON-7 study highlighted, with a HIGH quality, an absolute increase ranging from 6 to 64 thromboembolic events (point estimate: 26 events) per 1 000 cases.

d) Bleeding Grade ≥3
   I. The GOG-218 study reported, with a MODERATE quality (due to the scarcity of events and wide confidence intervals observed) an absolute difference that ranged from -1 to +51 episodes of bleeding (point estimate: 13 events) per 1 000 cases.
   II. The ICON-7 study highlighted, with a MODERATE quality (due to the low number of events observed) an absolute difference ranging from -2 to +16 episodes of bleeding (point estimate: 0 events) per 1 000 cases.
e) Quality of Life (QoL)
   I. In the GOG-218 study, bevacizumab patients reported lower FACT-O TOI scores than those in control arm during the chemotherapy phase of treatment (maximum difference: 2.9 points at the 4th cycle). From cycle 21, FACT-O TOI scores favoured the experimental arm (maximum difference in favour of bevacizumab: 2.0 points at 6 months) [49]. The smallest difference in FACT-O TOI score perceived by patients as important (Minimal Important difference – M.I.D. [50]), and that could lead clinicians to consider a change in the patient's management, was estimated to range between 5 and 8 points [49].
   II. The ICON-7 study reported a mean decrease over time of 2-3 points in the GHS index of the EORTC QLQ-C30 questionnaire, once again below the conventional M.I.D (>10 points [51]). Such a difference in score was recently [52] defined as Small (in a scale ranging from Trivial to Large [53]).

Bevacizumab in the treatment of advanced stage ovarian cancer: overall assessment of evidence

Due to the fact that in both studies examined the results obtained progressed in opposite directions (the addition of bevacizumab to standard CT was correlated to an improvement in terms of efficacy, but a worsening with regard to onset of adverse effects), overall quality was attributed taking the outcome obtaining the lowest quality evaluation as the most representative.

Overall quality for the GOG-218 study was MODERATE (Table 2).

Overall quality for the ICON-7 study is LOW if taken as a whole (ITT analysis, see Table 3); although it will prove to be MODERATE on taking into consideration the sole high-risk population (Table 4).

Bevacizumab in the treatment of advanced stage ovarian cancer: benefit/harm ratio

With regard to the target population (not fully resectable advanced stage ovarian cancer) the GOG-218 and the ICON7 study (high-risk subgroup) highlighted the following:

a) *benefit*: an improvement in critical outcomes PFS and OS, with an absolute reduction of 96 (GOG-218) – 103 (ICON-7) episodes of progression, and 40 (GOG-218) – 135 (ICON-7) deaths per 1 000 patients; the magnitude of this improved prognosis is clinically significant, particularly in the light of the prolonged lack of steps forward in this treatment area.

b) *harm*, a marked increase in risk of hypertension of Grade ≥3 (absolute increase of 59 episodes per 1 000 patients in the ICON-7 study, and 157 episodes in the GOG-218 study, respectively), the majority of which were controlled by means of appropriate treatment. The increased risk of other adverse events considered was negligible.

Thus, the positive effects produced should be viewed as taking prevalence over the negative effects (FAVOURABLE benefit/harm ratio).

CONCLUSIONS AND IMPLICATIONS FOR CURRENT CLINICAL PRACTICE

The addition of bevacizumab to the standard Cb-P combination has highlighted with an adequate degree of reliability (overall quality MODERATE) a FAVOURABLE harm-benefit balance.

Accordingly, the AIOM 2012 Guidelines recommend (SIGN grade A) the bevacizumab-Cb-P combination [54].

With regard to potential implications in current clinical practice, in the presence of an incidence rate of 4 900 new cases/year [12], it is estimated that 61% of these (2 989) will be diagnosed at stages IIIB, IIIC and IV [55]. Based on the findings of the IMS OncoTre 2010 study (unpublished data), 79% of the above patients (2 361) would be eligible for first-line treatment with Cb-P. Likewise, according to the findings of the same market research study, 83% of these patients (1 959) would be eligible for treatment with bevacizumab-Cb-P.

According with the previous pictures, the addition of bevacizumab to the standard Cb-P combination would produce an increase of about 80-265 surviving patients at 5 years at a cost of some between 120 and 310 extra-episodes of grade III hypertension.

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