Pharmacotherapeutic report bevacizumab (Avastin®) for the indication non-small cell lung cancer

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1. Summary

The Medicinal Products Reimbursement Committee has approved the pharmacotherapeutic report of the medicine bevacizumab (Avastin®) for non-small cell lung cancer (NSCLC). This medicine has been registered In combination with chemotherapy on the basis of a platinum compound, for the primary care treatment of what is characterised as non-operable and/or far advanced (stage IIIB/IV), non-squamous cell cancer-NSCLC.

The addition of bevacizumab to treatment with either carboplatin/paclitaxel or cisplatin/gemcitabine leads to an improvement in the response percentage. Combining bevacizumab (15 mg/kg) with carboplatin/paclitaxel lengthened the median general survival by two months (12.3 vs 10.3; HR: 0.80 [95% BI: 0.69-0.93]). This improvement may not be reached in women. The same applies to patients older than 65 years and patients who had lost a lot of weight prior to treatment. When a dose of 7.5 mg or 15 mg/kg bevacizumab is combined with cisplatin and gemcitabine, the treatment results in an improvement in median progression-free survival in comparison with treatment with only cisplatin/gemcitabine (HR[7.5]: 0.75 [95% BI: 0.62-0.91]; HR[15]: 0.82 [95% BI: 0.68-0.98]). With respect to general survival, however, on the basis of a provisional analysis, only the low dose seems to be effective. The use of bevacizumab in combination with a platinum doublet can lead to severe neutropenia, febrile neutropenia and infections. Other frequent severe side effects are hypertension, listlessness, tiredness, vomiting and nausea. Haemorrhage, one of the severe and sometimes life-threatening side effects characteristic of the use of bevacizumab, occurs relatively often in non-squamous cell cancer-NSCLC patients.

Final conclusion regarding therapeutic value
The addition of bevacizumab (15 mg/kg) to treatment with carboplatin/paclitaxel in patients with far-advanced (stage IIIB/IV) non-squamous cell carcinoma-NSCLC results in a clinically relevant extension in the duration of median progression-free and general survival. This means that this treatment has therapeutic added value in comparison with treatment with only carboplatin/paclitaxel. From the results of the study into the efficacy of bevacizumab in combination with cisplatin/gemcitabine, which are still provisional, the conclusion cannot be drawn that this treatment is more effective than treatment with only this platinum doublet. Together with the uncertainty about the optimum dose, the addition of bevacizumab to this doublet does not for the moment have therapeutic added value.

2. Introduction

Medicine	Bevacizumab
Composition	Bevacizumab, concentration for solution for intravenous infusion (25 mg/ml).
Registered indication	Bevacizumab, added to platinum-containing chemotherapy, is indicated for primary care treatment of patients with inoperable, far-advanced, metastasised or recidive non-small cell lung cancer, instead of with the predominant squamous cell histology.
Dose	7.5 or 15 mg/kg body weight, once per three weeks.
Mode of action	Bevacizumab is a recombinant humanised monoclonal antibody. Bevacizumab binds to vascular endothelial growth factor (VEGF). This interferes with the binding of VEGF to the VEGFR-1 (Flt-1) and VEGFR-2 (KDR) receptors present on the surface of endothelial cells. The reduced activity of VEGF interferes with the formation of

	blood vessels in tumours, which slows down tumour growth.
Particulars	In 2005 bevacizumab was registered, in combination with intravenous 5-fluorouracil and folic acid or intravenous 5-fluorouracil/folinic acid/irinotecan, for the primary treatment of patients with metastasised colonic or rectal carcinoma. The indication has been included in the policy regulation 'Expensive intramural medicines'. In 2007 bevacizumab was registered, in combination with paclitaxel, for the primary treatment of patients with metastasised breast cancer. CVZ has currently advised the NZa to include this indication in the policy regulation 'Expensive intramural medicines'. In November 2007 the CHMP issued positive advice regarding the application for the registration of bevacizumab in combination with alpha-2a interferon for the treatment of advanced or metastasised renal cell carcinoma.

For extensive information regarding this medicine, see the product text as published in the next edition of the *Farmacotherapeutisch Kompas* (see appendix 1).

3. Points of departure for assessment

3.a. Therapeutic area

Non-small cell lung cancer (or NSCLC) is one of the most frequently occurring malign diseases in the Netherlands. Lung cancer is diagnosed in more than 9,000 patients each year. This involves NSCLC in circa 80% of these cases, which occurs more often among men than among women (male-female ratio: 3.5:1). There are four main forms: squamous cell carcinoma, adenocarcinoma, large-cell and mixed small cell carcinoma. In addition, there are also mixed forms. Squamous cell carcinomas and adenocarcinomas occur most frequently (ca. 35 resp. 45%). For most patients (ca. 75%) NSCLC is only diagnosed when the disorder is already advanced locally or it has metastasised. The median survival upon diagnosis is about eight months. After five years only 13% of all patients are still alive. For patients with very-advanced NSCLC, this percentage is less than 5%. These statistics have only improved slightly over the years (CBO NSCLC Guideline 2004[1]; VIKC website, 1989-2004 data[2]; Socinski et al. 2003[3], 2007[4]; Cassidy et al. 2006[5]).

In its early stages (I-IIIA) the main treatment for NSCLC is with surgery and radiotherapy. Adjuvant chemotherapy, comprised of a platinum compound (cisplatin or carboplatin) in combination with gemcitabine, a taxane (docetaxel or paclitaxel) or vinorelbin, is increasingly being added to this treatment[1,3-5].

At a local far-advanced stage (IIIB) or where metastasis has occurred (IV), treatment is no longer curative but palliative and aimed at retaining quality of life, if possible using life-extending chemotherapy, whether or not in combination with radiotherapy[1,3-5]. Apart from supportive care, chemotherapy with a platinum compound (if possible at least 3 or 4 cycles)[1,3] is also being provided. In the USA, based on an expected improvement in the side effects profile, carboplatin (1x per 3 weeks) is used, particularly in combination with paclitaxel, docetaxel and gemcitabin[3,4] (Azzoli et al. 2007[6]). In Europe, on the other hand, cisplatin (1x per 3 weeks) is used more often, in combination with gemcitabine, docetaxel or vinorelbin[1,5]. The efficacy of these combinations is more or less the same, with a general survival lasting from nine to twelve months[1,3-5] (see pharmacotherapeutic report on vinorelbin, *Kompas*). A meta-analysis that was recently carried out, based on individual patient data from studies up to 2004, showed that the treatment results of cisplatin combinations are better than those of carboplatin combinations. This applies in particular to patients with NSCLC that is not related to squamous cell carcinoma. It also became clear that these combinations are not more toxic with respect to side effects[1,3-5] (Ardizzoni et al. 2007[7]; Letters[8]). Within this framework, the comment should be made that the doses of cisplatin,

gemcitabine and vinorelbin are currently lower than in the studies on the basis of which these products were introduced at the beginning of this century[1,3-5].

For patients with far-advanced NSCLC, the results of the chemotherapy applied largely depend on the (general) condition and on the stage of the disease[1,3-5]. The most important predictive parameter is the performance score (ECOG/WHO-PS; scores from 0 [=not hampered by the disease] to 4 [=extremely poor]; best treatment results for patients with a PS of 0 or 1)[1,3-5]. Other predictive parameters are age (result <65 years better than >65 years), results of previous treatment and loss of weight during the period prior to treatment[3,5].

3.b. Choice of comparative treatment

The comparative treatment is comprised of chemotherapy based on a platinum compound: cisplatin or carboplatin in combination with gemcitabine, a taxane or vinorelbin, in a three-weekly cycle. Accepted combinations in the Netherlands are cisplatin with gemcitabine, docetaxel or vinorelbin, or carboplatin with a taxane, or gemcitabine.

3.c. Method of assessment

For evaluation purposes the EPAR[9] and the IB text[10] were used, as well as study results that have been published in peer-reviewed journals. For the assessment a literature search was performed on 1st November 2007 (Med-line via PUB-Med, Embase and the Cochrane Library). Search terms (alone or in combinations): bevacizumab, cisplatin, carboplatin, docetaxel, paclitaxel, gemcitabine, vinorelbin, (squamous/non-squamous/bronchoalveolar) non-small cell lung cancer and NSCLC. The search supplied a number of additional references[3-7,16-18].

4. Therapeutic value

The therapeutic value of the combinations bevacizumab/carboplatin/paclitaxel and bevacizumab/cisplatin/gemcitabine was assessed according to the criteria efficacy, effectiveness, side effects, quality of life, experience, applicability and ease of use. The efficacy of antineoplastic products for the treatment of solid tumours is usually assessed according to four results (RECIST criteria): complete response (CR), partial response (PR), stabilisation (SD), and progression of the disease (PD) (Therasse et al. 2000[11]). The response percentage ('overall response rate') is the sum of the percentage of the complete response and the partial response[11]. (Median) time to progression and (median) progression-free survival apply as intermediary parameters for effectiveness. (Median) general survival applies here as definitive standard (CHMP guideline 2005[12]).

The first clinically significant results with bevacizumab (7.5 or 15 mg/kg, IV, every 3 weeks), added to a maximum of six three-weekly cycles of the standard combination carboplatin (IV, goal AUC of 6.0 mg/ml per min)/paclitaxel (IV, 200 mg/m^2) came from a randomised, open phase II study (Johnson et al. 2004[13]). This involved 99 patients with far-advanced NSCLC (largely stage IV and ECOG-PS 0 and 1), randomised respectively into treatment with a low (N=32) or a high (N=35) dose of bevacizumab/carboplatin/paclitaxel or with carboplatin/paclitaxel (N=32) alone. In the event of progression, only patients treated with carboplatin/paclitaxel could switch to treatment with bevacizumab alone at the highest dose[13]. In comparison with carboplatin/paclitaxel alone, the best treatment results were obtained with the high dose of bevacizumab, with a median administration of six cycles of carboplatin/paclitaxel. The median duration of survival was 17.7 months, in comparison with 11.6 months for the low dose and 14.9 for the patients treated with carboplatin/paclitaxel alone (incl. cross-over [n=19]). For the high dose of bevacizumab, the median time to progression was approximately seven months, for the low dose slightly more than four months. This last period did not differ from that of the control treatment[13]. As there were four cases of life-threatening pulmonary haemorrhages among the 13 patients with squamous cell carcinoma, in comparison with two of the 54 patients with adenocarcinoma[13] (see also 4.b.), bevacizumab was subsequently only studied among patients with non-squamous cell carcinoma, NSCLC[9,13] (Sandler et al. 2006[14]).

The efficacy and effectiveness of bevacizumab (7.5 and/or 15 mg/kg) in a fixed combination with three-weekly administrations of carboplatin/paclitaxel or cisplatin/gemcitabine were studied in two randomised, open phase III studies. The completed and published results of the American E4599-study with the combination bevacizumab/carboplatine/paclitaxel[14] formed the basis of the

European registration (in de VS bevacizumab [15 mg/kg] is only registered in combination with carboplatin and paclitaxel). Only provisional results are available from the study with bevacizumab/cisplatin/gemcitabine which was largely carried out in Europe.

In the E4599-study, treatment with a maximum of six cycles of the combination bevacizumab (15 mg/kg)/carboplatin/paclitaxel (NITT=434) was compared with treatment with a maximum of six cycles of carboplatin/paclitaxel (NITT=444) on patients with what was characterised as metastasised (ca. 75%) or locally advanced, inoperable (ca. 12%) non-squamous cell carcinoma-NSCLC. These were patients whose condition was still good, who had not previously been treated with chemotherapy in this stage of the disease. Patients with metastases in the central nervous system were excluded from participation. Treatment was continued until progression occurred. If treatment with bevacizumab/carboplatin/paclitaxel resulted in stabilisation or improvement, after a maximum of six chemotherapy cycles, treatment continued with bevacizumab alone. Stratification took place on the basis of risk-factors such as condition, weight loss prior to treatment, previous treatment with radiotherapy, stage of the disease, the presence of clear symptoms of the disease, gender, age (<65 vs ≥65 years), race, the number of places to which the disease had metastasised (≤2 vs >2), and the location of the metastasis (lungs, liver, skeleton, adrenal glands)[14]. The study's primary endpoint was median duration of survival. Secondary endpoints were response percentage, duration of the response and progression-free survival. The published results of the E4599-study relate to the completed study[14].

In the double-blind, placebo-controlled BO17704-study, treatment with a maximum of six cycles of the combination bevacizumab (7.5 or 15 mg/kg)/cisplatin/gemcitabine (NITT-7.5=345; NITT-15=351) was compared with a maximum of six cycles of placebo/cisplatin/gemcitabine (NITT=347). It involved patients with non-squamous cell carcinoma, metastasised or locally advanced and non-operable NSCLC and whose condition was still good, who had not previously been treated with chemotherapy in this stage of the disease. Patients with metastases in the central nervous system were excluded from participation. Treatment was continued until occurrence of disease progression. If the treatment with bevacizumab/cisplatin/gemcitabine resulted in stabilisation or improvement, after a maximum of six chemotherapy cycles, treatment continued with bevacizumab alone. The study's primary endpoint was median progression-free survival. Secondary endpoints were response percentage, (median) duration of the response, time to failure of treatment and duration of survival. The EPAR describes the results of a preliminary analysis which includes approximately half of the number of mortalities necessary for evaluating the secondary research parameter. No data are available on individual treatment groups (stratification). Definitive results are expected in 2008[9].

4.a. Efficacy

In the E4599-study, the median number of combination treatments was five (plus two cycles with bevacizumab alone for the patients treated with bevacizumab/carboplatin/paclitaxel). For patients in whom the disease could be assessed in advance, the response percentage of patients treated with bevacizumab/carboplatin/paclitaxel (29.0%) was considerably larger than for patients treated with only carboplatin/paclitaxel (12.9%; P <0.0001]) (Table 1)[9,14]. No data have been published about the composition of the response percentage (% CR, PR, SD or PD).

In the BO17704-study, the response percentage for treatment with bevacizumab in high or low doses and cisplatin/gemcitabine was, respectively, 33% (N=323) and 29% (N=332). A response percentage of 20% was calculated for the patients (N-324) treated with placebo/cisplatin/gemcitabine. In this group the treatment resulted only in a partial response. In the groups treated with bevacizumab, there was a complete response in, respectively, three (1%) and four patients (1%). In the latter groups, the median duration of the response was 6.1 months. In the control group the duration was 4.7 months[10].

Discussion: the response percentages found for treatment with respectively carboplatin/paclitaxel (E4599) and cisplatin/gemcitabine (BO17704) are exceptionally low[2-8]. Although the response percentage of carboplatin/paclitaxel in the E4599 study agrees with that of the study carried out by the same research group (E1594), and which served as point of departure and reference during registration (Schiller et al. 2002[15])[7,9], the response percentages of phase III studies carried out with comparable patient populations are actually at the level of the percentages found in the E4599 and BO17704 studies for the combination of bevacizumab with platinum doublets[2-8]. The cause of these differences is uncertain.

Conclusion: the efficacy of treatment with carboplatin/paclitaxel or cisplatin/gemcitabine is increased by the addition of bevacizumab. However, the response percentages for the combinations bevacizumab/carboplatin/paclitaxel and bevacizumab/cisplatin/gemcitabine hardly differ from the percentages usually found in comparable patient populations for treatment with only platinum doublets.

4.b. Effectiveness

Table 1 summarises the results of the E4599 and BO17704 studies in relation to median progression-free survival (PFS) and median general survival (OS).

Table 1. **Efficacy and effectiveness of bevacizumab in combination with carboplatin/paclitaxel (CARPAC) cisplatin/gemcitabine (CISGEM) on the basis of data published in the EPAR[10].**

Research-parameter	E 4599		BO17704		
	CARPAC	BEV 15/CARPAC	CISGEM	BEV 7.5/ CISGEM	BEV 15/ISGEM
Number of patients (ITT)	444	434	347	345	351
Response percentage (%)[1]	13[2]	29[2]	20	34	30
PFS HR (95% BI)		0.65 (0.56-0.76) P<0.0001		0.75 (0.62-0.91) P=0.0026	0.82 (0.68-0.98) P=0.0301
PFS duration (months - 95% BI)	4,8[2]	6.4[2]	NB	NB	NB
OS HR (95% BI)		0.80 (0.69-0.93)		0.88[3] (0.68-1.14)	1.02[3] (0.79-1.31)
OS duration (months)	10,3 (9.36-11.73)	12,3 (11.30-13.73)	NB	NB	NB
OS (% survivors after 1 year)	44	51	NB	NB	NB

NB: unknown.
[1] calculated over the number of patients with a proven disease (CARPAC: 392; BEV15CARPAC: 381; CISGEM: 324; BEV7,5CISGEM: 323; BEV15CISGEM: 332)[9].
[2] Sandler et al. (2006)[14] states for the ORR: 15% (CARPAC: 59/392) and 35% (BEV15CARPAC: 133/381) and for the PFS 4.5 (CARPAC) and 6.2 (BEV15CARPAC) months (HR 0.66: 95% BI:0.57-0.77).
[3] on the basis of approximately 50% of the number of mortalities that, according to the protocol, are required for determining general survival[9].

The improvement in the treatment results achieved by the combination bevacizumab/carboplatin/paclitaxel was also seen in the subgroups and high-risk groups[9,14]. However, on the basis of an explorative analysis, as far as the duration and survival is concerned, the treatment did not lead to better treatment results for women (HR: 0.89; 95% BI: 0.70-1.14), for patients aged older than 65 years (HR: 0.98; 95% BI: 0.77-1.25), patients with weight loss $\geq$ 5% upon initiation of treatment (HR: 0.85; 95% BI: 0.63-1.14), patients with metastases in the adrenal glands (HR: 0.97; 95% BI: 0.65-1.46) and patients with a vague histology[14]. No subgroup analysis is as yet available for the BO17704 study.

Conclusion: for previously untreated patients with far-advanced, non-squamous cell carcinoma-NSCLC, both median progression-free survival and general survival were approximately two months longer with the combination bevacizumab (15 mg/kg)/carboplatin/paclitaxel than for patients treated only with carboplatin/paclitaxel. The results of the E4599-study agree only partially with those of the BO17704-study. In spite of the clearly higher response percentage for both doses, on the basis of a provisional analysis of this study, only the combination treatment with the low dose of bevacizumab (7.5mg/kg) was more effective than treatment with cisplatin/gemcitabine alone. For this reason it is not clear which dose of bevacizumab leads to the best treatment results, and to which extent it is the choice of platinum doublet that determines the results of the treatment.

Discussion: in both the E4599 and the BO17704 studies, after completion of treatment with the platinum doublet, treatment continued – up until progression – with bevacizumab (median duration: 2 cycles). Due to the set-up of the studies, it is not clear whether the maintenance treatment with bevacizumab alone has a specific added value in comparison with the combined treatment with bevacizumab and the platinum doublet.

Irrespective of the type of NSCLC, in the event of metastasis, treatment with cisplatin or carboplatin in combination with gemcitabine, a taxane or vinorelbin (doublet therapy) has proven to be the most effective treatment of this disease[2-6]. The results achieved in the E4599-study, with carboplatin/paclitaxel for patients mostly with adenocarcinomas, are in keeping with results obtained in studies in which large groups of patients with both adenocarcinomas and squamous cell carcinomas participated[2-7,15]. In comparison with the results of most of the studies carried out with carboplatin/paclitaxel, the combination of bevacizumab/carboplatin/paclitaxel was more effective[2-7,15]. In only one study with carboplatin/paclitaxel (Ohe et al. 2007[15]) was the duration of the median general survival, 12.3 months, equal to that of the combination bevacizumab/carboplatin/paclitaxel.

Based on the results of the reference study[15] used for registration in the EU, in which no difference in effectiveness was found between carboplatin and cisplatin doublets, and the similarity between the hazard ratios of progression-free survival found for both bevacizumab combinations (the duration of the PFS for BO17704 is not mentioned in the EPAR), it was concluded that the choice of platinum compound is not what determines treatment results[9]. This conclusion is remarkable, as two other large, directly comparative studies, published at more or less the same time, showed that cisplatin doublets were more effective than carboplatin doublets (Rosell et al. 2002[17]; Fossella et al. 2003[18])[8]. This difference in effectiveness was recently confirmed, in particular for patients with adenocarcinomas, by the results of a meta-analysis of studies carried out on the basis of patient data, in which the carboplatin and cisplatin combinations were directly compared with one another[5,6]. Cisplatin/gemcitabine was also more effective than carboplatin/paclitaxel in the study of Ohe et al. (2007)[16] referred to above. Therefore it is quite likely that, in spite of the favourable treatment results of the combination bevacizumab/carboplatin/paclitaxel, these results will be no better than those of combination cisplatin/gemcitabine, whether or not in combination with bevacizumab.

A noticeable result of the explorative subgroup analysis of the E4599-study[14] is that with sizeable – albeit with overlaps – patient groups, namely women (ca. 50% of the study population) and patients who are older than 65 years (ca. 40% of the study population), the treatment with bevacizumab/carboplatin/paclitaxel was not more effective than the treatment with carboplatin/paclitaxel alone. As far as the treatment results of women is concerned, the reason for this is unclear. As such, for the use of platinum doublets, no differences in efficacy have been found between men and women and between the histologically different types of NSCLC[2-5]. It is generally known that older patients (> 65 years) and patients with a poorer condition (ECOG-PS: 2) often do not respond as well to treatment with a platinum doublet[2-7]. In agreement with slightly poorer treatment results among patients with a slightly poorer condition (ECOG-PS: 1)[14], a clearly discernable disease and a (multiple) metastasis (stage IV; >2 metastases) upon initiation of treatment[14], the combination of bevacizumab/carboplatin/paclitaxel also seems to be ineffective on patients who have lost a considerable amount of weight in the period prior to starting treatment[14].

Final conclusion: for patients with non-squamous cell carcinoma-NSCLC, the addition of bevacizumab to treatment with carboplatin/paclitaxel leads to a statistically significant and clinically relevant extension in the duration of general survival. This improvement may not be achieved in women. The treatment also seems to be ineffective for patients older than 65 years and those who have suffered major weight loss prior to treatment. In spite of the favourable effect on progression-free survival, it is not clear whether bevacizumab is actually effective when used in combination with cisplatin/gemcitabine and how the treatment effect of this combination compares with that of the bevacizumab/carboplatin/paclitaxel combination. Neither is the optimal dose of bevacizumab clear: for the moment, in combination with cisplatin/gemcitabine, a dose of 7.5 mg/kg seems to be more effective than a dose of 15 mg/kg. Lastly, no research has been carried out into whether it is advisable to continue treatment with bevacizumab after ceasing the chemotherapy.

4.c. Side effects

Reporting and evaluating side effects is only in relation to severe (non-haematological side effects) and very severe (haematological) side effects[9,14]. Due to the lack of uniformity in the way that the various studies register side effects, and the lack of published data on the BO17704-study, the discussion of side effects is limited to data presented in the EPAR[9].

All patient groups experienced, comparatively often (≥ 5%), tiredness, retching and nausea[9,14]. Shortness of breath and peripheral sensory neuropathy (paclitaxel)[19] was experienced in particular by patients treated with carboplatin/paclitaxel. On the other hand, listlessness, thrombocytopenia and anaemia was experienced in particular by patients treated with cisplatin/gemcitabine[9,10,14].

In comparison with treatment with carboplatin/paclitaxel or cisplatin/gemcitabine, the addition of bevacizumab to treatment led to a drastic increase in the number of patients with neutropenia, febrile neutropenia and/or infections. Other frequently reported (≥ 5%) side effects, specifically due to bevacizumab, were the occurrence of hypertension, nausea, retching and tiredness. Side effects observed relatively often (≥ 2%) among patients treated with bevacizumab/ carboplatin/paclitaxel were febrile neutropenia, infections, hyponatraemia and proteinuria[9,14]. Among patients treated with cisplatin/gemcitabine, the use of bevacizumab led particularly to thrombocytopenia, retching and nose-bleeds[9]. Hypertension and proteinuria have also often been observed among patients with other malign disorders who were treated with bevacizumab[9,10].

Although less frequently than among patients with squamous cell carcinoma[9,13], the use of bevacizumab among patients with non-squamous cell carcinoma-SNCLC, also led to more severe and sometimes fatal haemorrhages (specifically in lung tissue) than among patients treated only with chemotherapy (4-4.5 vs 2%)[9,13,14]. On the contrary, in comparison with studies for other bevacizumab indications (breast cancer/colorectal cancer), the incidence of both arterial and venous severe thromboembolic incidents was not increased – or hardly – among patients with lung cancer[9,10]. This also applies to the occurrence of gastrointestinal perforations and congestive heart failure[9].

Conclusion: the use of bevacizumab in combination with a platinum doublet leads in particular to the development of often severe neutropenia, febrile neutropenia and infections. Other frequently occurring severe side effects are hypertension, listlessness, tiredness, retching and nausea. Peripheral sensory neuropathy also occurs relatively often among patients treated with paclitaxel. Of the very severe and sometimes life-threatening side effects characteristic of the use of bevacizumab among patients with a non-squamous cell carcinoma- NSCLC, the only one to occur relatively often is haemorrhage.

4.d. Quality of life

No research has been done into the influence of treatment with bevacizumab in combination with carboplatin/paclitaxel or cisplatin/gemcitabine on the quality of life of patients with far-advanced lung cancer.

4.e. Experience

Throughout the world tens of thousands of patients have been treated for metastasised colorectal cancer and breast cancer since the registration of bevacizumab. Within the realms of research, hundreds of patients have been treated for – among other things – NSCLC, renal cell carcinoma, ovarial carcinoma and pancreatic and prostate cancer. Sufficient experience has been obtained with bevacizumab.

4.f. Applicability

According to the indication, bevacizumab may not be used for patients with squamous cell carcinoma-NSCLC. Bevacizumab may not be used before operations or 28 days after major operations or in cases where operation wounds have not yet completely healed. Neither may bevacizumab be used for patients with untreated metastases in the central nervous system. The risk of an arterial thromboembolic event occurring is increased among patients with a history of arterial thromboemboli or who are older than 65 years. The use of bevacizumab has not been studied among children and adolescents[9,10].

Conclusion: bevacizumab may not be used for patients with untreated metastases in the central nervous system or before and after operations or when operation wounds have not yet completely healed. The use of bevacizumab in elderly patients increases the risk of the occurrence of an arterial thromboembolic event.

4.g. Ease of use

Bevacizumab in combination with carboplatin/paclitaxel or cisplatin/gemcitabine is administered via intravenous infusion.

5. Other considerations

5.a. Costs

A total of 15 mg/kg bevacizumab is used per three-week cycle. For a patient weighing 70kg, this requires 1,050 mg bevacizumab per administration. Assuming the use of two flacons of 400 mg and three of 100 mg, the costs of bevacizumab amount to 2 x 1,350 plus 3 x 371.25 = 3,813.75 euro per cycle. If the recommended six cycles are administered, the costs amount to 22,882.50 euro (AIP excl. BTW). If 7.5 mg/kg is administered, the costs amount to 12,555 euro. For the treatment, the costs of bevacizumab need to be added to those of the chemotherapy. Additional costs will be incurred if treatment with bevacizumab alone is continued up until the time of progression after the recommended six cycles in combination with chemotherapy,.

6. Value of bevacizumab claimed by the manufacturer

6.a. Manufacturer's claim

Bevacizumab in combination with platinum-containing chemotherapy should be used as primary care treatment of non-squamous cell carcinoma-NSCLC that is inoperable or far-advanced (stage IIIB/IV).

6.b. CFH's opinion of the manufacturer's claim

The addition of bevacizumab (15 mg/kg) to the carboplatin/paclitaxel treatment of patients with far-advanced non-squamous cell carcinoma-NSCLC leads to a statistically significant and clinically relevant extension in the duration of general survival. This improvement may not be achieved with women. Neither do the results seem better than those of the control treatment for patients older than 65 years and those with severe weight loss prior to treatment. On the other hand, it is not clear whether treatment with bevacizumab in combination with cisplatin/gemcitabine is more effective than that with cisplatin/gemcitabine alone. There is also a lack of clarity about the optimal dose of bevacizumab: for the moment, in combination with cisplatin/gemcitabine, a dose of 7.5 mg/kg seems to be more effective than a dose of 15 mg/kg. The advisability of continuing treatment with bevacizumab after ceasing chemotherapy with a platinum compound has not been studied. The use of bevacizumab can lead to the occurrence of severe side effects which can sometimes be life-threatening. As the addition of bevacizumab to the combination carboplatin/paclitaxel does not seem to be effective – or hardly effective – for some groups of patients, the risk of these side effects occurring should emphatically be weighed up against the improvement in treatment affect that may be realised.

7. CFH-advice

Bevacizumab in combination with carboplatin/paclitaxel can be used during the primary care treatment of far-advance (stage IIIB/IV), non-small cell lung cancer that is characterised as non-squamous cell carcinoma.

8. Literature

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The data from this pharmacotherapeutic report will be incorporated into chapter 17 *of the* Farmacotherapeutisch Kompas.