HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
Focus
July 2016

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

AVASTIN (bevacizumab), monoclonal antibody

CERVICAL CANCER

Minor improvement in the treatment of persistent, recurrent or metastatic cervical cancer

Main points

- AVASTIN has Marketing Authorisation in adults with persistent, recurrent or metastatic cervical cancer, in combination with paclitaxel and cisplatin (or in combination with paclitaxel and topotecan in those who cannot receive platinum-based treatment).
- The addition of bevacizumab to chemotherapy has demonstrated a moderate effect on overall survival, but with reservations about the strength of the results and at the cost of accrued toxicity, especially recto-vaginal fistulas, compared to chemotherapy by carboplatin and paclitaxel.

Pre-existing indications*

AVASTIN also has Marketing Authorisation for other malignant tumours (ovary, breast, kidney, colon and rectum, lung).

Therapeutic use

Treatment of advanced stage cervical cancer (stage II to IV) is based on radiotherapy and radio-chemotherapy by cisplatin sensitivity. The optimal chemotherapy combination has not been defined, but the combination including cisplatin is considered standard treatment in Europe. Treatment based on carboplatin or medicinal products other than a platinum, in particular paclitaxel or topotecan, are considered therapeutic options in patients who cannot tolerate cisplatin.

Role of the medicinal product in the therapeutic strategy

The choice to prescribe bevacizumab requires consideration of the elevated frequency of adverse events, in particular ≥ 3 (76% with the addition of AVASTIN to chemotherapy compared to 58% with chemotherapy alone) and adverse events of particular interest such as gastrointestinal/vaginal fistulas (8.3% with AVASTIN versus 0.9% without AVASTIN), especially recto-vaginal. The patient should be informed of this information before treatment is started.

Clinical data

- An open-label, 4-arm randomized, parallel-group, phase III study evaluated, according to a 2x2 factorial design, the safety and efficacy of AVASTIN in combination with chemotherapy compared to chemotherapy alone in 452 patients with persistent, recurrent or metastatic cervical cancer.
  This study did not specifically include patients corresponding to the Marketing Authorisation for the combination of AVASTIN with topotecan/paclitaxel, in that the wording of the indication restricts this combination to patients who cannot receive platinum-based treatment (which is not the same as the inclusion criteria of this study).

  The median overall survival (primary endpoint) was not different between chemotherapy without platinum salts (topotecan-paclitaxel ± bevacizumab) and chemotherapy with platinum salts (cisplatin-paclitaxel ± bevacizumab): 13.3 months for the topotecan-paclitaxel combination (± bevacizumab) versus 15.5 months for the cisplatin-paclitaxel combination (± bevacizumab); stratified HR = 1.15; 95% CI [0.91; 1.46]; p = 0.2326.

* This summary does not cover these indications.

The median overall survival time was improved by 3.9 months in between the AVASTIN + chemotherapy group and the chemotherapy alone group: 16.8 months versus 12.9 months (stratified HR=0.74; 95% CI [0.58; 0.94], p<0.0132 < recalculated threshold 0.0140). However, this value (3.9 months) is probably overestimated because of the premature discontinuation of the study. There are reservations as to the strength of the results.

- The frequency at which treatment was discontinued because of adverse events was 26.1% in the AVASTIN + chemotherapy group (going up to 33% in the AVASTIN + cisplatin-paclitaxel subgroup) versus 18% in the chemotherapy alone group.
  The frequency of adverse events of particular interest (all grades) was higher in the AVASTIN + chemotherapy group compared to the chemotherapy alone group, in particular with an arterial hypertension grade ≥ 3 (respectively 11.5% and 0.5%), gastrointestinal perforations of all grades (respectively 3.2% and 0%), gastrointestinal/vaginal fistulas of all grades (respectively 8.3% and 0.9%) with primarily recto-vaginal fistula, bleeding grade ≥ 3 (respectively 7.3% and 4.5%), venous thromboembolic events grade ≥ 3 (respectively 10.6% and 6.3%).

Special prescribing conditions

- Medicine for hospital prescription.
- Prescription medicine restricted to cancer treatment and clinical oncology specialists.

Benefit of the medicinal product

- The actual benefit* of AVASTIN is substantial.
- In view of:

- a moderate gain in overall survival related to the addition of AVASTIN (bevacizumab) to chemotherapy in patients mostly with persistent or recurrent cervical cancer,
- but with reservations about the strength of these results (see paragraph 8.3 Summary and discussion),
- the accrued toxicity, especially recto-vaginal fistulas, related to adjuvant use of AVASTIN,

the addition of AVASTIN to chemotherapy with paclitaxel and cisplatin (or topotecan in case of ineligibility for platinum salts) provides a minor improvement of actual clinical benefit** (IACB IV) compared to this chemotherapy.

- Recommends inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 6 July (CT-15038) and is available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.
** The improvement of actual clinical benefit (IACB) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of IACB on a scale from I (major) to IV (minor). A level V IACB (equivalent of “no IACB”) means "no clinical added value".