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Original article

Evaluation at 3 years of concurrent bevacizumab and radiotherapy for breast cancer: Results of a prospective study

Évaluation à 3 ans de l'association de radiothérapie et bévacizumab pour le cancer du sein : résultats d'une étude prospective

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ABSTRACT

Purpose. – To determine the 3 years late toxicity among patients with non-metastatic breast cancer who received concurrent bevacizumab and locoregional radiotherapy.
Material and methods. – This is a single-arm, multicentre, prospective study, of the toxicity of adjuvant concomitant association of bevacizumab and radiotherapy in patients with breast cancer. Toxicity was assessed by the Common Terminology Criteria for Adverse Events version 3.0 during the radiotherapy and follow-up clinics at 12 and 36 months after its completion. The study was designed to evaluate the toxicity at one year, 3 years and 5 years.
Results. – Sixty-four patients were included from October 2007 to August 2010. All of them received concurrent adjuvant radiotherapy and bevacizumab (in 24 cases after primary systemic treatment). All patients received non-fractionated radiotherapy to breast or chest wall with or without irradiation of regional lymph nodes. Early toxicity has been previously reported. Median follow-up was 46.4 months (range: 18–77 months). Median age was 53 years old (range: 23–68 years). The 3-years overall survival was 93% (range: 87–100%). Evaluation of the toxicity at 3 years was available for 67% of the patients. There was a low rate of toxicity: 14% grade 1 pain, 9% grade 1 fibrosis, 2% grade 1 telangiectasia, 2% grade 1 paresis, 7% grade 1 lymphedema and 2% grade 3 lymphedema. No grade 4 toxicity was observed. No patient had a left ventricular ejection fraction below 50% at 3 years.
Conclusions. – Concurrent bevacizumab with locoregional radiotherapy is associated with acceptable 3-years toxicity in patients with breast cancer.

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RÉSUMÉ

Objectifs de l'étude. – L'objectif de cette étude prospective, multicentrique, à un bras, était d'étudier la tolérance à 3 ans d'un traitement adjuvant associant radiothérapie et bévacizumab en concomitance, chez des patientes atteintes d'un cancer du sein non métastatique.
Matériel et méthodes. – Cette étude a inclus des patientes participant à des études sur le rôle du bévacizumab dans le traitement néoadjuvant et/ou adjuvant du cancer du sein localisé. La radiothérapienormofractionnée du sein ou de la paroi et l'irradiation ganglionnaire a été délivrée lorsque indiquée. L'évaluation a été réalisée à 12 et 36 mois de la fin du traitement.
Résultats. – Soixante-quatre patientes ont été incluses d'octobre 2007 à août 2010. Elles recevaient un traitement adjuvant associant le bévacizumab et la radiothérapie. La tolérance aiguë avait fait l'objet d'une publication précédente. Le suivi médian était de 46,4 mois (extrêmes : 18–77 mois). L'âge médian était de 53 ans (extrêmes : 23–68 ans). La probabilité de survie à 3 ans était de 93 % (extrêmes : 87–100 %). La tolérance a pu être évaluée à 3 ans pour 67 % des patientes. Il y avait 14 % de douleurs de grade 1, 9 % de fibroses de grade 1, 2 % de télangiectasies de grade 1, 2 % de troubles neurologiques de grade 1, 7 % et lymphœdèmes de grades 1 et 2 % de lymphœdèmes de grade 3. Aucune patiente n'avait de fraction d'éjection du ventricule gauche inférieure à 50 % à 3 ans.
Conclusion. – L'association de concomitante de radiothérapie et de bévacizumab adjuvant chez des patientes prises en charge pour un cancer du sein a été bien tolérée à 3 ans.

1. Introduction

Neoangiogenesis is a key factor in tumour growth and metastasis development. Vascular endothelial growth factor (VEGF) is the main neoangiogenesis growth factor in breasts tumours [1]. Bevacizumab (Avastin®, Genetech Pharmaceuticals, San Francisco, CA) is a humanized monoclonal antibody targeting circulating VEGF, thus preventing the tumour from creating neovessels. Bevacizumab has shown encouraging results in combination with chemotherapy in the treatment of various metastatic tumours, including breast tumours [2]. There is also a rationale for is use of concomitant bevacizumab and radiotherapy, as inhibiting VEGF also leads to a transient normalization of the tumour oxygenation, minimizing the hypoxia which is an important factor of decreased radiation sensitivity [3].

The clinical trials BEVERLY I, BEVERLY II, BEATRICE and BETH have been conducted to investigate the use of bevacizumab as a neoadjuvant and/or adjuvant treatment for non-metastatic breast cancer [4–7]. Published results of the randomized phase III trial BEATRICE, testing bevacizumab as an adjuvant therapy for breast cancer, showed that this regimen had no effect on invasive disease-free survival among triple-negative breast cancer [4]. No clinical benefit of the addition of bevacizumab was observed in the BEVERLY-1, BEVERLY-2 and BETH study either [5–7].

Few data are available on the concomitant use of bevacizumab and radiotherapy in the treatment of breast cancer. For the treatment of lung cancer or pancreatic cancer, the association of bevacizumab and radiotherapy has shown significant toxicity [8,9], although for other tumours such as cervical cancer this association can be well tolerated [10].

As the tolerance of this association was not specifically studied in the BEATRICE, BEVERLY-1, BEVERLY-2 and BETH studies, the TOLERAB study was designed. To investigate the tolerance of this association, we enrolled the patients treated in France with concurrent bevacizumab and adjuvant radiation therapy from those studies in the TOLERAB study from October 2007 to August 2010.

We present here the late toxicity (at 3 years) and cosmetic result of concurrent bevacizumab and locoregional breast radiotherapy as reported in the TOLERAB study, as acute and one year toxicity have been the subject of a previous publication [11].

2. Materials and methods

2.1. Patient screening

The French multicentric non-interventional, single-arm observational cohort TOLERAB study included, from October 2007 to August 2010, patients with non-metastatic breast cancer treated by local or locoregional radiotherapy and concurrent bevacizumab as previously described [11,12]. The patients received either neoadjuvant or adjuvant chemotherapy in the trials BEVERLY 1, BEVERLY 2, BEATRICE or BETH (Fig. 1). All patients gave written informed consent.

2.2. Endpoint

The goal of this study was to assess the tolerance of the concomitant association of bevacizumab and radiotherapy in the adjuvant treatment of breast cancer. Statistical comparison was not planned

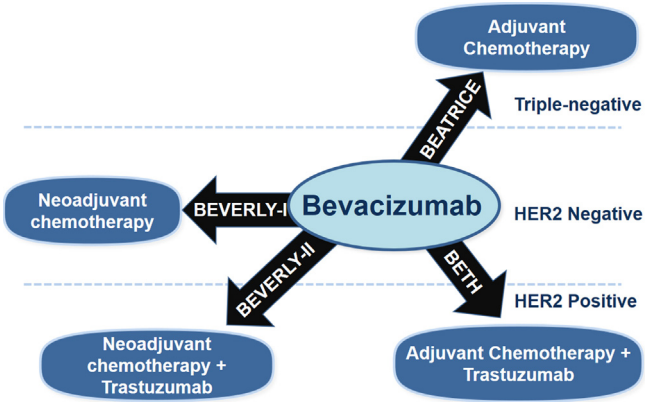

Fig. 1. Single-arm, multicentre, prospective study, of the 3-year toxicity of adjuvant concomitant association of bevacizumab and radiotherapy in patients with breast cancer: presentation of clinical trials on bevacizumab with concurrent radiotherapy and description of the patient population.

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