Pathol. Oncol. Res. (2013) 19:119–122
DOI 10.1007/s12253-012-9551-7

METHOD

Successful Treatment of Solitary Bone Metastasis of Non-Small Cell Lung Cancer with Bevacizumab and Hyperthermia

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Received: 1 September 2011 / Accepted: 31 May 2012 / Published online: 3 July 2012

Abstract Non-small cell lung cancer (NSCLC) represents 85 % of all malignant lung cancers. In metastatic disease the principle goal of palliative therapy is to prolong survival with least toxicity and best patients' quality of life. Bevacizumab (BEV) has been approved as first line treatment in combination with platinum based chemotherapy and maintenance therapy in NSCLC. BEV can be added safely to several chemotherapeutic agents, however there is no data on coadministration with thermotherapy. Even in localized disease no robust evidence exists about the beneficial effect of loco-regional thermotherapy on overall survival, but it might be used successfully in symptom palliation. In this article a successful co-administration of BEV and hyperthermia is reported in a patient with monolocalized bone metastasis from previously operated NSCLC. This case suggests that electrohyperthermia can probably be incorporated in palliative therapy added not only to radiotherapy or chemotherapy but also to anti-angiogenic BEV treatment.

Keywords Solitary bone metastases · Lung cancer · Hyperthermia · Bevacizumab

Introduction

Approximately 85 % of lung cancers are non-small cell lung cancer (NSCLC) half of them being adenocarcinomas [1]. Most of NSCLCs are diagnosed in an advanced stage or become metastatic during the natural course of the disease [2, 3]. The standard first line strategy for the treatment of advanced stage NSCLS is a limited number of chemotherapy cycles to achieve tumor regression or at least stabilization [4].

In general, the median survival with such chemotherapy is 7 months. The addition of bevacizumab (BEV) to cisplatin-based chemotherapy significantly prolonged progression free survival and overall survival in phase III [5, 6] and phase IV trials [7], proved to be safe treating over 5000 patients [8–10] and in the maintenance setting also demonstrated its beneficial effect on PFS [11, 12].

Hyperthermia combined with radiotherapy and chemotherapy, seems to be a promising method for cancer treatment. Its mode of action has been reviewed previously [13], although many of the underlying molecular mechanisms of this combination treatment remain poorly understood even today. Preliminary results in NSCLC recruiting limited number of patients (N:5-80) also seem encouraging where hyperthermia was combined with chemotherapy, radiotherapy or both. The co-administration of hyperthermia was demonstrated to be safe [14–17].

A number of studies show that hyperthermia inhibits angiogenesis, enhances chemo- and radio-sensitivity and induces high concentrations of drugs within the tumour [18, 19]. Although it is a logical extension of the above outlined experience, to our knowledge, there is no published data on the co-administration of thermotherapy and the anti-angiogenic agent BEV.

In this case a loco-regional deep electro-hyperthermia system called oncothermia was used [20].

Presentation of the Case

In an asymptomatic 64 year old male patient with no significant past medical history, a screening chest radiograph

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captured a solitary lung lesion. He had been a heavy smoker with a 50 pack-year history, and only discontinued smoking when the disease was diagnosed. Laboratory investigations did not reveal any relevant abnormality. The initial staging CT showed no other lesions in the thorax, abdomen or pelvis. Cranial MR ruled out intracranial involvement. Transthoracal fine needle aspiration disclosed a poorly differentiated adenocarcinoma. Right upper lobectomy was performed at our institution in February 2008. The histological examination reported a 38 mm adenocarcinoma with metastatic spread to one of two resected hilar lymph nodes. The adenocarcinoma was poorly differentiated with different areas variably showing bronchiolo-alveolar or acinar, papillar and solid characters. Extensive necrosis and vascular invasion were also described in the pathology report and surgical margins were free of tumor. Tumor DNA was found to harbor a mutation in exon 2 of the K-RAS gene, but not in exon 19 or 21 of the EGFR gene. The patient declined the offered adjuvant chemotherapy and was followed every 3 months. Chest-abdomen CT scans showed no evidence of disease until May 2009 when solitary (hip bone) osseal metastasis appeared on CT scan. An MRI and a bone scan confirmed the presence of metastatic bone disease. The patient remained asymptomatic.

From July 2009 through November 2009 six cycles of combination chemotherapy consisting of paclitaxel (175 mg/m2)+carboplatin (400 mg/m2) and BEV (7.5 mg/kg) was given every 3 weeks, resulting in disease stabilization (Fig. 1). Zoledronic acid was concomittantly administered, as well from the start of chemotherapy. BEV was continued as maintenance therapy after completion of the six cycles of chemotherapy (7,5 mg/kg every 3

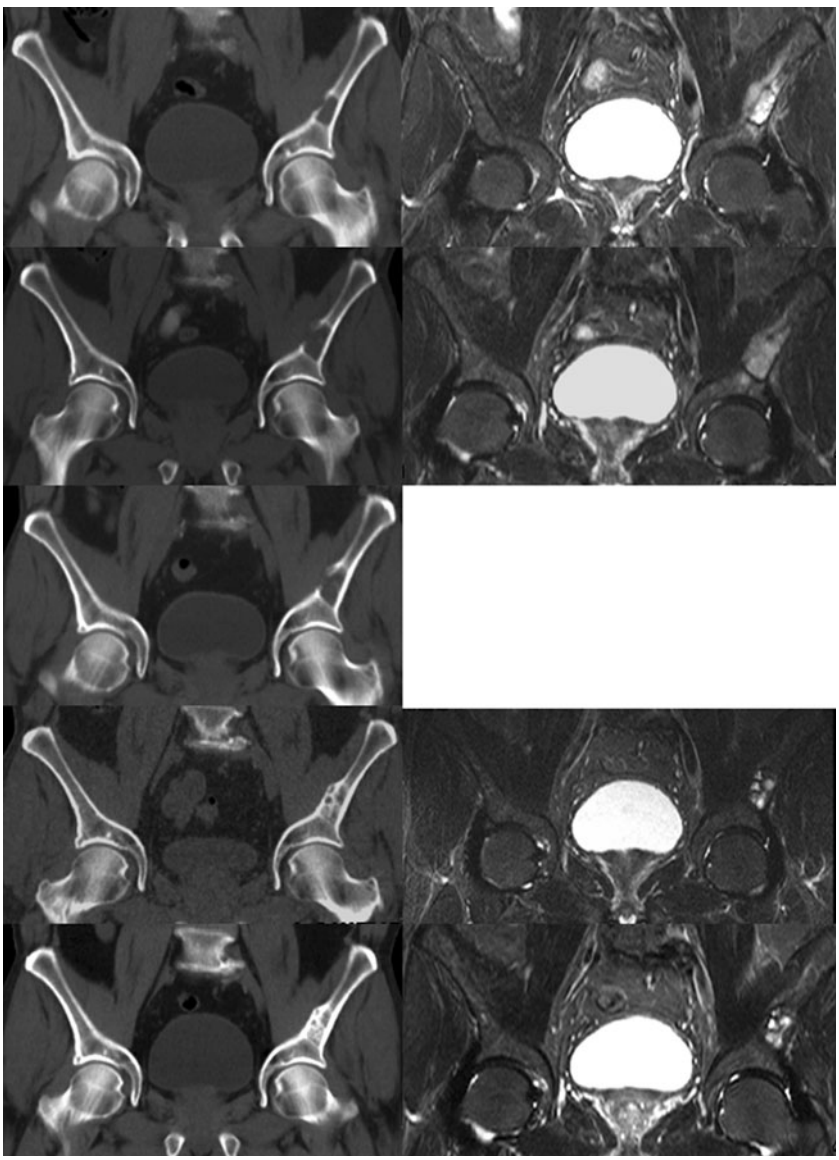

Fig. 1 MDCT with coronal reconstruction—(left column) and T2-weighted fat suppressed MR images (right column). **a.** (first row): Images were obtained in May and June, 2009. New, osteolytic bone lesion was detected, with partial cortical destruction above the left hip. Solitary bone metastasis was revealed. **b.** (second row): first control examination after a period of chemotherapy in August 2009. Osteolytic destruction became more prominent. **c.** (third row): only CT has been made right before starting oncothermia near the end of chemotherapy in October 2009. No significant change compared to the previous image. **d.** (fourth row): after half a year of bevacizumab and oncothermia co-administration in May 2010, osteoplastic bone reconstruction can be seen due to regression of disease. **e.** (fifth row): after one year of bevacizumab and oncothermia co-administration in December 2010, the condition is unchanged

weeks). Tumor size measurement (CT and MR) was performed every 6–8 weeks during BEV maintenance therapy following a nation-wide protocol.

Oncothermia was added to maintenance BEV at the beginning of November 2009. The device used was EHY2000® (OncoTherm, Troisdorf, Germany). It operates at 13.56 MHz, which is time-domain (fractal) modulated, with 40–150 W power absorbed by the tumor. A 20 cm applicator was used over the affected region. Patient received oncothermia three times a week, treatment time per session was 60 min with the maximal tolerated dose of 70 W.

From March to May of 2010 oncothermia was suspended. Until January 2011 in 14 months 125 sessions of oncothermia were added to BEV treatment. During this time period osteoplastic bone reconstruction was captured in CT scans and his only metastasis diminished and later stabilized in size (from 37 mm to 24 mm). The patient remained painless. Since that time no new adverse event emerged, and we continued to deliver oncothermia, BEV maintenance therapy and zoledronic acid concomitantly.

Discussion

Our patient had a very favorable response to applied therapy which contained the combination of BEV and oncothermia. It could not be determined which component of therapy had role in anti-tumoural effect, although the evaluation of CT and MRI images suggested that the regression became evident during combination therapy of oncothermia, BEV and zoledronic acid. He may be one of the few patients whose disease responds perfectly to systemic treatment, however, his bone metastases was mono-localized, which is rare in stage IV NSCLC and this made the situation ideal for loco-regional treatment. In this case, loco-regional oncothermia might have contributed to the beneficial effect. As far as we know there are only two reports of solitary bone metastases of NSCLC in the literature [21, 22].

The EGFR and K-RAS mutation status are well established biomarkers for anti-EGFR tirosine-kinase inhibitors but no connection with bevacizumab efficacy has been demonstrated so far. However, for efficacy of bevacizumab we have no accepted predictive marker. In an exploratory analysis of 45 patients the lower early post-treatment level of VEGF predicted improved efficacy in NSCLC [23]. In another analysis on 63 SCLC patients the low vascular cell adhesion molecular level predicted higher efficacy [24]. In both one arm trials it was not clarified whether the prediction refers to bevacizumab or the chemotherapy. Phase 3 trials could give us more information on biomarkers like the BeTa trial [25].

This case demonstrated that hyperthermia can be well tolerated and safely combined with the targeted biological anti-angiogenetic agent BEV. To our knowledge there is no report on efficacy or safety of hyperthermia co-administered with BEV so far, although hyperthermia itself has anti-vascular effect, too. Considering the excellent safety profile of hyperthermia, it may be suggested that patients who could not tolerate combined chemo-radiotherapy or for whom it is contraindicated, gain the most from the addition of hyperthermia. The best mode of integration of hyperthermia in the treatment of NSCLC needs further investigation. In this case, oncothermia seemed not to compromise BEV efficacy and their co-administration was safe, encouraging further investigation of this combination in advanced NSCLC.

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