Cetuximab is an active treatment of metastatic and chemorefractory thymoma

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1. ABSTRACT

Advanced chemorefractory thymic epithelial tumors still represent a challenge in clinical oncology. A rationale-based therapeutic approach targeting a key pathway should represent the ideal solution in a neoplasm that can over-express Epidermal Growth Factor Receptor (EGFR) in the epithelial component. On the basis of these considerations, two patients with metastatic heavily pretreated disease were evaluated for EGFR expression in the primitive tumor, being considered this data as a basis for an anti EGFR treatment with the monoclonal antibody cetuximab which targets EGFR. A strong EGFR expression was revealed by immunohistochemistry in the two cases considered, thus the patients received cetuximab and reported a partial response as assessed by Computed Tomography (CT), Positron Emission Tomography (PET) and fused PET-CT after three months of therapy. Therefore, both patients are still on therapy. This preliminary experience suggests that cetuximab may be a useful therapeutic choice in advanced pre-treated thymic tumors.

2. INTRODUCTION

New approaches are currently investigated for advanced chemorefractory thymic epithelial tumors. Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. The EGFR family is a group of four structurally similar growth factor receptors with tyrosine-kinase activity (EGFR, HER2/neu, ErbB-3, ErbB-4), which dimerize upon binding with a number of ligands, including EGF (Epidermal Growth Factor) and TGF (Transforming Growth Factor), allowing downstream transduction of mitogenic signals. Activation results in a variety of cellular responses including cell proliferation and differentiation. Tyrosine kinase oncogenes represent an appealing anti-tumor drug target since they play a fundamental role in a variety of cellular responses including cell proliferation and differentiation. In clinical trials, anti-EGFR is showing promise in the treatment of solid tumors expressing EGFR (1-3). Neoplastic thymoma cells express EGFR (4,5). We evaluated the clinical activity of Cetuximab, a chimeric human-mouse monoclonal IgG1 antibody blocking ligand
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binding to EGFR, in two cases of advanced chemorefractory thymic epithelial tumors.

3. MATERIALS AND METHODS

3.1. Patient Characteristics and response evaluation

For patient characteristics see Case report 1 and 2 in the Results section. Given the progressing refractory disease, both the patients were assessed for EGFR expression in the primary tumor, being considered this data as a basis for an anti EGFR treatment. Both the patients were evaluated as concerns clinical status and biochemistry and were imaged by a combined PET-CT.

3.2. Morphological and Immunohistochemical Methods

The tumours were re-evaluated according to the criteria of the WHO classification (1999) of Thymic tumours (6) and of the 2004 classification of thymic tumours (7). The immunohistochemical study was performed by an EGFR pharmDx assay - a qualitative immunohistochemical kit system – identifying EGFR (HER1) protein in EGFR-expressing cells (DakoCytomation, Carpenter, CA) according to the manufacturer’s instructions in routinely fixed, paraffin embedded material. Staining of the tumor cell membrane above the background level was considered positive (+). Staining intensity was graded 1+ , 2+ or 3+ according to the manufacturer’s instructions. To validate the staining runs, negative control reagent was used in place of the primary antibody according to the instructions.

3.3. Treatment schedule

EGFR expression showed by neoplastic epithelial cells in the paraffin material from both tumours was considered a support for an anti EGFR treatment in vivo. The patients provided informed consent and Local Ethical Committee approved the administration of the drug. Both patients received intravenous cetuximab (C225, Erbitux, Merck KgaA, Darmstadt, Germany) over 1 hour at 400 mg/m² during the course of 1 hour. Premedication with an antihistamine was given according to the recommendations. For the initial dose, the infusion period was 120 minutes. For the subsequent weekly maintenance doses, the infusion period was 60 minutes. Patient evaluation was performed monthly through clinical and laboratory routine examination. The patients n.1 and n.2 started the treatment in November and December 2004, respectively. The first PET-CT evaluation was performed after three months of treatment. The patients were maintained on therapy in the absence of disease progression or unacceptable toxicity.

4. RESULTS

4.1. Case report 1

In 1993, a 36-year-old previously healthy woman presented a combined B2/B3 thymoma according to WHO classification of Thymic Epithelial Tumours (1999) (7) staged III by Masaoka (8). After neoadjuvant PEC (platinum, epidoxorubicin, cyclophosphamide) chemotherapy, she underwent surgical resection of the thymic mass and thereafter received further adjuvant chemotherapy with the same scheme and local radiotherapy (30 Gy). In 1998 a paravertebral relapse at level of D12-L1 vertebrae was shown by Magnetic Resonance Imaging (MRI) and was pathologically confirmed as a metastasis of the same thymic tumour. The patient underwent surgical resection of this metastasis and adjuvant radiotherapy (44 Gy). Three years later, the patient relapsed again in the paravertebral region. Moreover, bone, lung and liver metastases were found. A somatostatin analog-based therapy was started because of patient’s refusal of conventional chemotherapy, according to previous described patient’s inclusion criteria and therapy schedule (9). A slight reduction of paravertebral relapse and stable disease in the other sites was maintained for about two years. Because of liver toxicity the therapy was stopped and the disease progressed. Therefore, the patient started a chemotherapy regimen including platinum, which was stopped soon because of an allergic reaction.

4.2. Case report 2

In 1990, a 34-year-old man suffering from myasthenia gravis underwent surgical resection of B3 thymoma according to WHO ’99 classification (6) staged III by Masaoka (8) and following adjuvant radiotherapy. Eight years later multiple pleural nodules were shown. The patient was surgically treated and received chemotherapy (platinum and etoposide). In 1999, he underwent surgery again because of a paravertebral relapse of thymoma at level of D8 vertebra causing medullary cord compression and thereafter received radio- and chemotherapy (cyclophosphamide, vincristine and procarbazine). In 2001, a chest Computed Tomography documented a mediastinal cystic mass measuring 4.5 cm at longest diameter. Moreover, pleural solid tissue was visualized in front of middle lung lobe. Positron Emission Tomography (PET) showed uptake in all these sites including the cystic mass. The patient started a somatostatin analog-based therapy and reported disease stabilization until November 2004 when a progressing paravertebral lesion was discovered. Surgery was considered unfeasible because of significant risk of paralysis.

4.3. Morphologic and immunohistochemical revision

Case n. 1 corresponded to a combined B2/B3 thymoma, and case 2 was considered a B3 thymoma according to the criteria of the 1999 (6) and 2004 (7) WHO classifications of Thymic Tumours. For the EGFR staining, in case n.1 slides of the primary tumor and of a synchronous lymph node metastasis were available, for case n. 2 only material from the primary tumor was available.

The two cases considered were both extensively and strongly membranous positive, graded 2+ in the sections considered. Only epithelial cells reacted, thymoma lymphocytes being unreactive. In Figure 1 staining of case n.1 was shown.

4.4. Clinical responses

After three months of therapy, both the patients achieved a partial response as assessed by CT, PET and
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**Figure 1.** Case 1 Strong membranous positivity for EGFR in B2 thymoma epithelial cells. Lymphocytes are unreactive. 200x

**Figure 2.** Coronal whole-body [18F]FDG scans of the patient before and after therapy (first row), showing changes of tracer uptake at different metastatic sites. Transaxial slices of CT, PET and fused PET-CT scans at the level of the upper lobe of the right lung (second and third row) showing changes of standardized uptake value (SUV) max before and after therapy.
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Table 1. Changes of standardized uptake value (SUV) max in different metastatic sites.

<table>
<thead>
<tr>
<th>Site</th>
<th>Nov 2004</th>
<th>Feb 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right lung</td>
<td>6.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Right paravertebral</td>
<td>7.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Left paravertebral</td>
<td>6.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Left para-aortic</td>
<td>7.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
<td>3.0</td>
</tr>
<tr>
<td>Sub-costal</td>
<td>5.2</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Figure 3. Transaxial slices of CT, PET and fused PET-CT scans before and after therapy showing changes of FDG uptake at the level of the right paravertebral metastasis (arrow), left paravertebral metastasis (arrow head facing upward), para-aortic metastasis (oblique arrow head), liver and sub-costal metastases.

In conclusion, this preliminary evaluation suggests for the first time that cetuximab may be a useful therapeutic choice in advanced pretreated thymic tumors. Despite the need for prolonged follow-up of the patients and further confirmatory studies, the EGF/EGFR pathway seems to play a pivotal role in thymic tumors.

6. ACKNOWLEDGEMENTS

This work was partially granted from the Italian Ministry of Health, Progetti Ricerca Finalizzata 2002.

7. REFERENCES

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Key Words: thymoma, Epidermal Growth Factor, Epidermal Growth Factor Receptor, Cetuximab, Metastatic, Chemo-Refractory

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