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Adverse pulmonary reactions associated with the use of monoclonal antibodies in cancer patients

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Summary
Background: The incidence and clinical characteristics of adverse pulmonary reactions resulting from anticancer monoclonal antibody (mAbs) therapy have not been well described. We determined the incidence and clinical characteristics of adverse pulmonary reactions in patients treated with anticancer chemotherapy including mAbs.
Methods: A retrospective cohort study was performed including patients who were treated with a chemotherapeutic regimen that included rituximab, trastuzumab, cetuximab, or bevacizumab at Seoul National University Hospital between January 1, 2004 and December 31, 2008. Rates of adverse pulmonary reactions classified as non-infectious and infectious complications were compared with those among patients treated with comparable regimens without mAbs.
Results: In total, 1078 patients were included (418 for rituximab, 329 for trastuzumab, 122 for cetuximab, 209 for bevacizumab). Adverse pulmonary reactions were identified in 36 patients (3.5%) and the incidence differed among agents: cetuximab (9%), rituximab (5.3%), trastuzumab (0.6%), bevacizumab (0.5%). Infectious pulmonary complications occurred in 28 patients, and eight patients experienced non-infectious pulmonary complications, most commonly interstitial lung disease (6 patients). In a multivariate analysis, low serum albumin level was associated with the development of pulmonary complications. The incidence of overall adverse pulmonary reactions did not differ between the mAbs users and the 1012 patients treated with comparable regimens other than mAbs (3.5% vs. 2.8%, $P = 0.53$).

Abbreviations: EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; NHL, non-Hodgkin's lymphoma; mAbs, monoclonal antibodies; VEGF, vascular endothelial growth factor.

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Conclusions: Infectious and non-infectious adverse pulmonary reactions occur in patients with cancer who are administered a regimen including mAbs. Clinicians should be alert for the possibility of pulmonary adverse reactions, particularly among patients with low serum albumin levels.

Introduction

New anti-neoplastic agents are constantly being added to the list of available treatments for various cancers.[1,2] Among them, biological agents are one of the most promising modalities to combat cancers and other diseases.[3] In fact, more than 20% of the compounds approved by United States regulatory authorities over the last 5 years were biological agents.[4] Representative new anti-neoplastic biological agents are monoclonal antibodies (mAbs), which bind specifically to target cells. By blocking specific cell receptors, mAb therapy destroys malignant tumor cells and prevents tumor growth.[5]

For example, rituximab, which targets the CD20 receptor, is widely used for $CD20^{+}$ non-Hodgkin's lymphoma (NHL).[6] Cetuximab, which binds to the epidermal growth factor receptor (EGFR), has shown efficacy in patients with colorectal, head/neck, and non-small cell lung cancers.[7] As with other anticancer drugs, adverse pulmonary events associated with mAbs can occur, including dyspnea, pulmonary embolism, pneumonia, interstitial lung disease, and pleural effusion.[6–11]

In this study, we determined the incidence and clinical characteristics of adverse pulmonary drug reactions in patients treated with anticancer chemotherapy including mAbs in combination with other agents or as monotherapy.

Materials and methods

Study population

A retrospective cohort study was performed with patients who were treated with a chemotherapeutic regimen included rituximab, trastuzumab, cetuximab, or bevacizumab at Seoul National University Hospital between January 1, 2004 and December 31, 2008. Patients, older than 18 years, who were being treated for their cancer with the aforementioned mAbs, were included. Patients lost to follow-up immediately after the first chemotherapy session were excluded. For comparison, patients treated with comparable regimens without mAbs were also included: CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone) users as counterparts of rituximab users, Taxol users as counterparts of trastuzumab users, and FOLFOX (oxaliplatin, leucovorin, and 5-fluorouracil) or FOLFIRI (irinotecan, leucovorin, and 5-fluorouracil) users as counterparts of cetuximab and bevacizumab users. The Ethical Review Committee of our institution approved the protocol for this study.

Clinical data review

Patient clinical data, including medical records, radiographic findings, and laboratory results were reviewed.

Definition of adverse pulmonary reaction

New respiratory symptoms or abnormal radiographic/laboratory results that developed after mAb use were reviewed as possible adverse reactions. Two of the authors (HJ Kang and JS Park) reviewed the data independently. If their opinions on the presence of an adverse pulmonary reaction differed, another author (JJ Yim) made the decision. Adverse pulmonary reactions were divided into non-infectious and infectious complications, based on a previous study.[1]

Non-infectious complications

- Hypersensitivity with bronchospasm
  - Defined as bronchospasm plus other hypersensitivity-related symptoms (angioedema, rash, urticaria, hypotension, arthralgia, nausea, vomiting, hypotension, or hypertension).
- Drug-induced interstitial lung disease
  - Clinical and radiographic manifestations compatible with interstitial pneumonitis.
    - ➢ Clinical manifestations including dry cough, dyspnea, and fever.
    - ➢ Radiographic findings such as diffuse ground-glass opacity, reticular shadows, or consolidation without segmental distribution and a honeycomb pattern with no evidence of underlying heart disease, infection, or other pulmonary disease.

- Noncardiogenic pulmonary edema.
  - Diagnosed when pulmonary edema was not associated with heart failure or increased left atrial pressure.
- Acute lung injury.
  - Noncardiogenic pulmonary injury associated with evidence of acute inflammation, such as fever and elevated neutrophils in broncho-alveolar lavage fluid.
  - Diffuse bilateral pulmonary infiltrate with no evidence of elevated left atrial pressure and a PO_2/FiO_2 ratio <300.
- Acute respiratory distress syndrome.
  - Diffuse bilateral pulmonary infiltrate with no evidence of elevated left atrial pressure and a PaO_2/FiO_2 ratio <200.

Infectious complications

- Symptoms of an acute lower-respiratory tract illness (cough and at least one other lower-respiratory tract symptom).
  - New focal chest signs on examination.