Infectious complications of monoclonal antibodies used in cancer therapy: a systematic review of the evidence from randomized controlled trials

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CRD summary
The authors concluded that the use of rituximab in the treatment of non-Hodgkin lymphoma does not appear to influence infection rates, except for HIV-positive patients. Trastuzumab appears to slightly increase grade III-IV infections in the treatment of breast cancer. In view of the limited search and failure to assess study validity, these conclusions may need to be considered with some caution.

Authors' objectives
To determine the risk of infection associated with the use of monoclonal antibodies (MoAbs) for the treatment of cancer.

Searching
PubMed was searched for articles published up to August 2006; the search terms were reported. The reference lists of retrieved articles were checked. The search was restricted to studies reported in English or German.

Study selection
Randomised controlled trials (RCTs) reporting infectious complications associated with MoAbs were eligible for inclusion, provided the MoAbs were approved by the Food and Drug Administration and were administered either alone or with chemotherapy or radiation therapy to patients with haematological or solid malignancies. Controls were required to receive a regimen not containing MoAbs. Studies utilising radioimmunoconjugates were excluded.

The most common forms of cancer addressed in the included studies were non-Hodgkin lymphoma and breast cancer, though there were also studies of patients with diffuse large-B cell lymphoma, chronic lymphocytic leukaemia, lung cancer, colorectal cancer, and head and neck cancers. The MoAbs used included rituximab, alemtuzumab, trastuzumab, bevacizumab and cetuximab. These were administered with conventional chemotherapy regimens or radiotherapy; controls received chemotherapy or radiotherapy alone, or observation. The outcomes in the review were the infection rate (overall, grade I-II, grade III-IV) and infection-related death.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Results were reported as the percentage experiencing the event in each group, with p-values for differences between the groups in some cases.

Two reviewers independently extracted the data, with any disagreements resolved in discussion with a third reviewer.

Methods of synthesis
The studies were combined in a narrative with accompanying evidence tables, organised by type of malignancy and type of drug regimen used.

Results of the review
Twenty RCTs (n=9,411) were included in the review.

Haematological cancers (10 RCTs, n=3,131).
There were 6 RCTs of rituximab combined with cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) versus CHOP alone. Three RCTs reported similar infection rates in both groups. One RCT found a lower rate of grade III-IV infection in the RCHOP arm (12% versus 20%) and another found a higher rate of infection-related deaths in the RCHOP arm (1.5% versus 1%). The sole RCT conducted among human immunodeficiency virus (HIV)-positive patients found a significantly higher infection-related death rate in the RCHOP arm (14% versus 2%, p=0.035).

There were 4 RCTs of other comparisons. No significant differences were found between the groups when rituximab with non-CHOP chemotherapy was compared with non-CHOP chemotherapy alone (3 RCTs). In one small RCT (n=21), patients receiving alemtuzumab (only) had a 70% increase in total infections compared with controls receiving observation.

Solid cancers (10 RCTs, n=6,280).

There were 5 RCTs of trastuzumab for primary breast cancer. Five RCTs reported on the use of trastuzumab for primary breast cancer. In comparisons of trastuzumab plus chemotherapy versus chemotherapy alone (4 RCTs), RCTs reported higher rates in most MoAb arms of grade I-II infection (2.8%, 3.9%, 1 RCT, 2 comparisons), grade III-IV infection (0.9% ,1 RCT) and overall infections (6%, 15.2%, 18%, 3 RCTs). However, infection-related deaths were 2% higher in the control arm in one comparison (1 RCT). An RCT (n=3,387) of trastuzumab versus observation reported higher rates of grade III-IV infection (0.9%) and overall infections (1.1%) in the MoAb arm.

There were 5 RCTs of MoAbs for other solid cancers. Comparisons of bevacizumab plus chemotherapy versus chemotherapy alone reported higher overall rates of infection in the MoAb arms of 3 RCTs, two of which had both low- and high-dose arms (1%, 6%/10% and 5%/20%, respectively). However, grade III-IV infections were only 0 to 1% higher in the MoAb arm (1 RCT). Two RCTs comparing cetuximab with chemotherapy or radiotherapy versus chemotherapy or radiotherapy alone reported a 1.9% increase in overall infection rates and a 5% increase in grade III infections (respectively) in the MoAb arms.

Authors’ conclusions
The use of rituximab in the treatment of non-Hodgkin lymphoma does not appear to influence infection rates, except in HIV-positive patients. Trastuzumab appears to slightly increase grade III-IV infections in women being treated for breast cancer.

CRD commentary
The review question and inclusion criteria were clear. The search was limited to one database and was restricted by language, and unpublished studies do not appear to have been specifically sought. This means that studies might have been missed and the review may be subject to publication and language biases. Steps were taken to minimise error and bias in the review by having more than one reviewer independently make decisions on the study selection and data extraction processes. However, it does not appear that study validity was systematically assessed. Lack of information about important aspects of validity (e.g. allocation concealment, blinding, follow-up rates) makes it difficult to determine the reliability of the evidence presented. In view of the limited search, potential for publication and language bias, and failure to assess study validity, the authors’ conclusions may need to be considered with some caution.

Implications of the review for practice and research
Practice: The authors stated that physicians should be aware of the potential risk of infection associated with MoAbs as new MoAbs become available in clinical practice. They recommend increased surveillance when administering rituximab to HIV-positive patients with non-Hodgkin lymphoma, especially if the CD4 cell count is low.

Research: The authors did not state any implications for research.

Funding
Not stated.

Bibliographic details

PubMedID
17429839

DOI
10.1002/cncr.22666

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal /adverse effects; Antineoplastic Agents /adverse effects; Humans; Neoplasms /immunology /therapy; Opportunistic Infections /etiology; Randomized Controlled Trials as Topic; Risk Factors

AccessionNumber
12007001938

Date bibliographic record published
01/04/2008

Date abstract record published
01/12/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.