Cancer Treatment Reviews 41 (2015) 859–867

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

The use of combinations of monoclonal antibodies in clinical oncology

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ARTICLE INFO

Article history:
Received 10 July 2015
Received in revised form 21 October 2015
Accepted 23 October 2015

Keywords:
Monoclonal antibody
Oncology
Combination therapy
Review

ABSTRACT

Treatment with monoclonal antibodies is becoming increasingly important in clinical oncology. These antibodies specifically inhibit signaling pathways in tumor growth and/or induce immunological responses against tumor cells. By combining monoclonal antibodies several pathways may be targeted simultaneously, potentially leading to additive or synergistic effects. Theoretically, antibodies are very suitable for use in combination therapy, because of limited overlapping toxicity and lack of pharmacokinetic interactions. In this article an overview is given of preclinical and clinical data on twenty-five different combinations of antibodies in oncology. Some of these combinations have proven clinical benefit, for example the combination of trastuzumab and pertuzumab in HER2-positive breast cancer, which exemplifies an additive or synergistic effect on antitumor activity in clinical studies and the combination of nivolumab and ipilimumab, which results in significant increases in progression-free and overall survival in patients with advanced melanoma. However, other combinations may lead to unfavorable results, such as bevacizumab with cetuximab or panitumumab in advanced colorectal cancer. These combinations result in shorter progression-free survival and increased toxicity compared to therapy with a single antibody. In summary, the different published studies showed widely varying results, depending on the combination of antibodies, indication and patient population. More preclinical and clinical studies are necessary to unravel the mechanisms behind synergistic or antagonistic effects of combining monoclonal antibodies. Most research on combination therapies is still in an early stage, but it is expected that for several tumor types the use of combination therapy of antibodies will become standard of care in the near future.

Introduction

Monoclonal antibodies are becoming increasingly important in the field of oncology. These antibodies are modified proteins, aimed to target a specific part of deregulated signal transduction pathways in a tumor. Other antibodies have been developed to interfere with immunological processes in the human body. In several tumor types, the use of a monoclonal antibody has become standard of care.

Besides the development of new monoclonal antibodies, much attention is paid to combination therapies of monoclonal antibodies. In many tumors more than one signaling transduction pathway is deregulated. Monoclonal antibodies generally target only a single transduction pathway. Blockade of such a pathway often has only limited effect, because tumors can overcome this hindrance by shifting to other pathways. By combining monoclonal antibodies, however, it is possible to simultaneously block two signaling transduction pathways, resulting in an additive or even synergistic effect against tumor growth. A similar mechanism accounts for monoclonal antibodies that function as immune checkpoint inhibitors; when these antibodies are combined the immune system is activated by more than one pathway to target tumor cells, which can lead to increased anti-tumor activity.

In general, monoclonal antibodies have limited overlapping toxicity, which enables safe administration of two monoclonal antibodies. Furthermore, few to no pharmacokinetic interactions are expected between antibodies that are administered concurrently. These advantages make combining antibodies an attractive strategy. Often it is possible to administer the same dosages in combination therapy, as used in monotherapy. However, while

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http://dx.doi.org/10.1016/j.ctrv.2015.10.008
0305-7372/

many combination therapies are under investigation, only few have yet been approved.

In this review, we aim to address several important issues related to the success or failure when combining monoclonal antibodies. An overview is given of the published preclinical and clinical research on combination therapies with monoclonal antibodies.

Methods

A literature search was conducted in the PubMed database to identify relevant studies. The search term *monoclonal antibody [tiab] AND combination [tiab] AND (cancer [tiab] OR oncology [tiab]*) was used, results were screened for relevance, and thereafter for each combination of antibodies an additional search was conducted with the search term *"antibody 1" [tiab] and "antibody 2" [tiab]*, to look for additional relevant publications. Literature up to May 2015 was included.

Results

To our knowledge, publications on twenty-five different combinations of monoclonal antibodies for oncological and malignant hematological indications have been published so far. An overview of all publications on these twenty-five combinations is provided for solid tumors (Table 1) and hematological malignancies (Table 2) respectively. For each combination, details are given on indication, type of research and the most important results of the published studies.

Preclinical studies

In general, as can be seen in Tables 1 and 2, relatively few preclinical studies with combination of monoclonal antibodies are published, compared to studies on clinical studies.

An example of a combination that was investigated in a preclinical setting as the basis for clinical trials, is the combination of trastuzumab and pertuzumab. In HER2 positive breast cancer, the human epidermal growth factor receptor 2 (HER2) is activated and then dimerization occurs. Dimerization can occur with other HER2 receptors (homodimerization), but also with other types of HER receptors, such as HER3 (heterodimerization). The antibody trastuzumab targets HER2 and through this blockade, signal transduction is inhibited. However, heterodimerization of HER2 with HER3 can still occur, therefore, not all growth stimulating signals of tumor are completely inhibited. The addition of pertuzumab, a monoclonal antibody that inhibits heterodimerization of HER2 and HER3 by targeting the dimerization domain of HER2, could be theoretically useful [1–3]. Nahta et al. showed that combining pertuzumab with trastuzumab resulted in a synergistic effect on cell death of a breast cancer cell line with HER2-overexpression [3]. Also for other indications where HER2 is involved, combining pertuzumab and trastuzumab appears to lead to favorable results. An increased antitumor activity compared to monotherapy was found for ovarian cancer [4], endometrial cancer [5] and gastric cancer [6].

Also for the combination of cetuximab and bevacizumab preclinical research has been performed. These antibodies target important interconnected signaling routes involved in several types of cancer: cetuximab the epidermal growth factor receptor (EGFR) and bevacizumab the vascular endothelial growth factor (VEGF). Wang et al. described a mouse model for head and neck squamous cell carcinoma where this combination was investigated. In this study, it appeared that triple therapy (cetuximab, bevacizumab and cisplatin) resulted in less delay in tumor growth and worse survival compared to bevacizumab and cisplatin alone. This study, therefore, argues against the combination of the two monoclonal antibodies [7].

For many other combinations described in Tables 1 and 2, no published preclinical data are available. As almost all monoclonal antibodies are first studied in humans as monotherapy and are found to be safe before use in clinical studies on the use of combination therapy, this might implicate that combination studies are not supported by further preclinical data. However, preclinical models may still be useful to predict potential non-additive or antagonistic effects of a combining strategy, as described above for the combination of cetuximab and bevacizumab.

Clinical trials

As seen in Tables 1 and 2 several combinations of monoclonal antibodies have been studied in various stages of clinical development. The first antibody combination to be approved was the combination of trastuzumab and pertuzumab in breast cancer. The largest study on this combination is the CLEOPATRA-trial. This is a randomized phase III-trial in HER2-positive metastatic breast cancer. In total, 808 patients were randomized to receive trastuzumab plus pertuzumab plus docetaxel or trastuzumab plus placebo plus docetaxel. The group receiving both trastuzumab and pertuzumab had a median progression-free survival of 18.5 months, while this was 12.4 months in the group receiving trastuzumab plus placebo [8]. Also overall survival was significantly improved, with a median overall survival of 56.5 months in the group receiving the combination and 40.8 months in the group receiving trastuzumab [9]. The safety profile, including cardiac toxicity, was comparable between monotherapy and combination therapy [8,10].

A second very promising antibody combination is therapy with both ipilimumab (targeting cytotoxic T-lymphocyte associated antigen (CTLA-4)) and nivolumab (targeting the receptor for programmed cell death (PD-1)). These two antibodies, both immune checkpoint modulators, are used for treatment of advanced melanoma. CTLA-4 and PD-1 appear to play complementary roles in regulating immune response. Based on this mechanism, these two antibodies were combined in several trials including a recently published phase III-study [11]. In this trial the combination was compared both with ipilimumab monotherapy and with nivolumab monotherapy in a total of 945 patients. The median progression-free survival was 11.5 months in patients receiving nivolumab plus ipilimumab, compared to 2.9 months for ipilimumab monotherapy and 6.9 months for nivolumab monotherapy, which shows persuasively that the combination has superior clinical activity. However, treatment-related adverse events were also significantly increased in the group receiving both nivolumab and ipilimumab, compared to patients receiving monotherapy. In the combination group 55.0% of the patients experienced grade 3 or 4 treatment-associated adverse events, while this was 16.3% in the group receiving nivolumab and 27.3% for ipilimumab. The most frequent severe adverse events were diarrhea, increase in alanine aminotransferase levels and colitis [11]. Based on these clinical results, the U.S. Food and Drug Administration granted approval for nivolumab in combination with ipilimumab.

Also for hematological tumors, clinical trials investigating combining monoclonal antibodies have been performed. For example, the combination of rituximab and alemtuzumab has shown promising activity. Rituximab targets CD20 on B-cells and alemtuzumab CD52. Both drugs are effective in the treatment of chronic lymphocytic leukemia and the combination of the two antibodies appeared to be safe and effective as shown in three phase II-trials [12–14]. However, in another phase II-trial by Badoux et al. in patients with relapsed chronic lymphocytic leukemia, an increased infection rate was observed and no benefit in