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Therapeutic antibodies against cancer

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Abstract

Antibody-based therapeutics against cancer are highly successful in clinic and currently enjoy unprecedented recognition of their potential; 13 monoclonal antibodies (mAbs) have been approved for clinical use in the European Union and in the United States (one, mylotarg, was withdrawn from market in 2010). Three of the mAbs (bevacizumab, rituximab, trastuzumab) are in the top six selling protein therapeutics with sales in 2010 of more than $5 bln each. Hundreds of mAbs including bispecific mAbs and multispecific fusion proteins, mAbs conjugated with small molecule drugs and mAbs with optimized pharmacokinetics are in clinical trials. However, challenges remain and it appears that deeper understanding of mechanisms is needed to overcome major problems including resistance to therapy, access to targets, complexity of biological systems and individual variations.

Keywords

therapeutics; antibodies; cancer; immunogenicity; safety; efficacy

1. Introduction

Antibody therapy has its roots thousands of years ago; early forms of vaccination against infectious diseases were developed in China as early as 200 BC. However, the history of true antibody therapy began much more recently with the discovery that serum from animals immunized with toxins, for example, diphtheria toxin or viruses, is an effective therapeutic against the disease caused by the same agent in humans. This discovery resulted in the development of the serum therapy which saved thousands of lives; von Behring who in the 1880s developed an antitoxin that did not kill the bacteria, but neutralized the toxin that the bacteria release into the body was awarded the first Nobel Prize in Medicine in 1901 for his role in the discovery and development of a serum therapy for diphtheria. Interestingly, although historically successes of antibody (serum) therapy were initially mostly in the treatment of patients with infectious diseases currently there is only on monoclonal antibody (mAb) approved for treatment of any infectious disease (synagis) and it is for prevention of the infection not for therapy of already established infection. Initial attempts to treat cancer patients with serum therapy were not successful. It was not until several decades ago when a

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number of revolutionary scientific discoveries were made that allowed the development of recombinant therapeutic resulting in the approval of the first anti-cancer therapeutic antibody – mAb rituximab in 1997 (Table 1). Since than 13 mAbs have been approved for clinical use against cancer in the European Union and the United States and 12 are on the market in August 2011; one of them, Gemtuzumab ozogamicin (Mylotarg), was withdrawn (Table 1); in contrast we still have to wait for the first approved mAb-based therapeutic against an infectious disease (synagis is for prevention). In 2010 sales of the top four recombinant therapeutic antibodies (bevacizumab, rituximab, trastuzumab, cetuximab) exceeded US$ 20 bln (Table 2).).

Dating back to mummies and up to the recent successes with ipilimumab it has become axiomatic that the human immune system has an inherent capacity for anti-tumor activity. This was bolstered in the 1900s by the finding of spontaneous remissions recorded—often in sparse anectodal findings-- in nearly ever stage and form of cancer, by the more common observation of spontaneous regressions of melanoma and renal carcinoma, the success of non-specific immune-stimulants such as BCG or Coley's toxin and the increasingly targeted use of antibodies against antigens more specific to certain cell types [1]. Indeed, the antibody specificity was perhaps the first and still the most powerful story supporting the ubiquitous catch-call of personalized medicine.

With all of the elegance of the specificity story and more than 35 years since Kohler and Milstein's recipe for generating monoclonal antibodies [2], the clinical promise has been largely disappointing. With rare exceptions, these molecular missiles have not annihilated their target tumors and have fallen far short of the marvel of the antibiotic revolution. The rarity of cures should not dampen the substantial, if incremental, progress that has been made. Even in the age of single nucleotide etiologies there is a strong case that cancer, by the time of its clinical visibility, consists of many broken parts; hence the growing argument that targeted therapies may parallel the breakthrough to cure with chemotherapy in the 1970's with the move to, not one, but a cocktail of simultaneous, combined agents. As in the case of combination chemotherapy, antibody therapy may come to utilize different effector pathways in this assault.

Therapeutic mAbs and other therapeutic proteins have been reviewed previously (see recent reviews [3–15] and articles cited there). Therefore, here, we review the monoclonal antibodies used directly in treatment, shed some light on presumed primary mechanism of action, and survey use—from initial indication to the wider adoption based principally on clinical trials and trends. This line-up, with its wide spectrum of targets and mechanisms may give some hope yet that the long trek may yet reach the originally envisioned summit. If not, these agents are undoubtedly part of the solution. We focus mainly on those native, unconjugated antibodies that directly impact solid tumors. Bevacizumab, though its anti-vascular action is indirect, has gained such wide application for solid tumors (and been subject of much controversy) that it seemed important to include. Finally, while immune-conjugates have been well reviewed elsewhere [16–18] and not the present focus brentuximab vedontin, as the first new indication for Hodgkin's in 30 years warranted special inclusion. Its success represents a partial rescue of a paradigm after the first approved antibody-drug conjugate, gemtuzumab was withdrawn in 2010 due to lack of efficacy and increased deaths [19]. In the context of the present review it may also point to some limiting aspects in unconjugated tumor-directed antibodies, which as has been stated, have not delivered their quarter-century promise.

2. mAbs approved for clinical use

Currently, (as of August 2011) 13 mAbs are approved for clinical use in the European Union (EU) or United States (US) (Table 1). One of the approved mAbs, gemtuzumab ozogamicin (Mylotarg) was withdrawn from the market because of lack of clinical benefit and safety reasons after a clinical trial in which a greater number of deaths occurred in the group of patients with acute myeloid leukemia (AML) who received Mylotarg compared with those receiving chemotherapy alone. Mylotarg as well as removab which is not approved in the USA yet, and the two radiotherapeutic mAbs, Bexxar and Zevalin, will not be reviewed here.

2.1 Rituximab

The first candidate out of the starting box remains in many ways the poster child for both specificity and efficacy. Rituxamab (MabThera, Rituxan), initially developed in San Diego in the late 1980's, and father to that regions biotech explosion, was based upon the finding of CD20 antigen on normal and malignant lymphocytes; it is not appreciably expressed at either pole of lymphocyte ontogeny--stem cells and plasma cells--nor on other non-lymphoid cellular compartments. In contrast to many emerging cancer targets clearly connected with signal transduction circuitry there is no clear consensus on the function of CD20. Nonetheless, the chosen antigen-antibody duo in CD20/rituximab rendered a striking clinical success and ushered in a continuing wave of similarly conceived agents albeit with variant tactical goals and mechanisms of effect. It is interesting to note that only after many years afterward were clinical agents developed to target perhaps the ultimate tissue-specific bull's eye: the individual epitope of each B lymphocyte population—separating the malignant fiend from over a million brethren lymphocytes by one signature antigen expressed on one malignant subspecies.

In 1997 rituximab was approved by the US FDA for treatment of relapsed indolent B-cell non-Hodgkin's lymphoma. The antibody is a mouse-human chimera utilizing murine variable regions to effect anti-CD20 specificity and human IgG1k constant region to facilitate effector function including complement mediated lysis and antibody directed cellular cytotoxicity [20, 21]. Additional mechanisms include caspase activation [22] a “vaccinal effect” based upon increased idiotype-specific T cell response to follicular lymphoma [23], and upregulation of proapoptotic proteins such as Bax [24, 25].

Its well-known, early recognized and sometimes fatal chief toxicity has been acute infusion reactions. Rare fatalities, occurring mainly during first infusion, have been considered secondary to a cytokine reaction; generally associated with flu-like symptoms they may progress to life threatening hypotension, bronchospasm and hypoxia, but can usually be controlled by stopping or adjusting of rates of infusion and proper premedication [26]. Blackbox events include tumor lysis syndrome, severe mucocutaneous reactions and progressive multifocal leukoencephalopathy (PML) resulting in death [27, 28].

Rituxumab has demonstrated clinical activity across the spectrum of lymphoproliferative disorders but the greatest impact has been in non-Hodgkin's lymphoma, where combinations and optimizations, have sought to raise response rates and ultimately cure. Since its 1997 start with relapsed indolent non-Hodgkin's lymphoma (NHL), rituximab has obtained the following additional indications for lymphoma per package insert: relapsed and refractory, follicular or low-grade, CD20-positive, B-cell NHL as single agent; previously untreated CD20-positive, follicular, B-cell NHL in combination with first line chemotherapy; as single agent maintenance therapy for patients achieving a partial or complete response to rituximab in combination with chemotherapy; for non-progressing (including stable), CD20 positive, low-grade, B-cell NHL, as a single agent after first-line combination of cyclophosphamide,

vincristine, and prednisone (CVP) chemotherapy; previously untreated CD20 positive, diffuse large B-cell NHL in combination with anthracycline-based chemotherapy, for example, in the workhorse, R-CHOP [29]. It also has an oft-used indication for treatment of previously treated or untreated patients with CD20 chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC) [30].

It has found off-label use in the clinic in all or nearly all malignant (and many non-malignant) settings where B-cells are presumed to participate in pathogenesis and been the subject of many scholarly reviews. Common use spans from aggressive to low grade lymphoproliferative disorders including: combination with chemotherapy for induction in second line therapy for relapsed lymphoma anticipating autologous transplant [31]; combination with chlorambucil for indolent and with bendamustine in treatment of relapsed or refractory CLL [32]; induction for Burkitt's, use for gastric and non-gastric mucosa-associated lymphoid tissue (MALT tumors [33, 34], Mantle cell tumor [35], primary cutaneous B-cell [36], splenic marginal zone NHL [37] Waldenström's macroglobulinemia/ lymphoplasmacytic lymphoma [38]. Its uses have been tailored to mutational status of del(17p) and del(11q) with refractory CLL (National Comprehensive Cancer Network (NCCN) guidelines - http://www.nccn.org/index.asp) and combined in “cocktail” with other antibodies such as alemtuzumab for refractory lymphoid malignancies.

The evolution of treatment for CLL mirrors, in many ways, that of NHL as it leads from purines to chemo-immunotherapy and most recently to novel antiCD20 antibodies. Conventional treatment of CLL evolved from alkylators to purine analogues when it was demonstrated that fludarabine (F) yielded greater efficacy with better complete response (CR), progression-free and overall survival (PFS and OS) rates than chlorambucil as primary therapy [39]. Subsequently, the combination of fludarabine with cyclophosphamide (FC) showed better CR and PFS than F [40]. Based upon the activity of rituximab (R) alone as a front line agent, it was added to FC and compared to FC alone; in a phase III randomized trial the combination FCR demonstrated better OR, CR, and PFS, establishing both the regimen and the concept of chemo-immunotherapy in this setting as the upfront standard of care [41].

2.2 Ofatumumab

Unfortunately, the activity of rituximab as a single agent is only modest [42] and duration of response in relapsed disease is generally measured in months [43]. This was part of the impetus to develop newer anti-CD20 targeted antibodies with a goal to improve such characteristics as binding affinity, specificity and effector function, and efficacy [44]. Ofatumumab (ofa), a fully human monoclonal IgG1 binds to a unique epitope [45], induces considerably higher complement dependent cytotoxicity (CDC) than rituximab [46] and shows activity in rituxan-refractory B cell lymphoma [47].

On the basis of these potential biological advantages and modest early phase clinical activity [48] ofa was tested against CLL which was either refractory to fludarabine and alemtuzumab or refractory to fludarabine with disease considered too bulky for efficacy with alemtuzumab [49]. The drug was well tolerated, though complicated by infections in 25% of the patients, but the impressive clinical results including median OS of 13.7 or 15.4 months, within two high risk groups, respectively, contributed to the approval of ofa for disease refractory to fludara and for those who have failed alemtuzumab [50, 51].

Given the potential advantages of ofa versus rituximab and FCR established as standard of care in front line, substituting ofa for rituxan in the so-call O-FC regimen was tested in a multinational, randomized phase II trial in treatment naïve patients [52]. Of the two tested doses, the higher dose arm yielded a CR rate of 50%. It remains unclear how to position this

with respect to such other findings as the initial randomized phase III trial that established FCR as standard of care. The precedent of combining permutations of purine analogues, alkylators and antibodies including newer regimens like Ofa/bendamustine continues to inform ongoing studies [53].

2.3 Ipilimumab

The novel treatment agents for melanoma, vemurafenib (b-raf inhibitor) and ipilimumab (an antibody against cytotoxic T lympocyte antigen 4 (CTLA-4)), represent perhaps the most significant advance in oncology in several years. How they will fit in tactical treatment strategies, and with respect to conventional dacarbazine, IL-2, and a new gp100 based vaccine is a welcome and exciting challenge after decades without appreciable progress [54]. Blockade of the CTLA-4 has been the subject of long and intensive investigation [55, 56].

Among the most active immune inhibitory pathways is the CD28/CTLA-4:B7-1/B7-2 receptor/ligand grouping which modulate peripheral tolerance to tumors and outgrowth of immune-evasive clones. Inhibition is both toward the overexpressed self targets via upregulation of inhibitory ligands on lymphocytes. Thus blockade of CTLA-4 has potential for both mono-therapy and in synergy with other therapies that enhance presentation of tumor epitopes to the immune system [56]. Genetic ablation of CTLA-4 leads to a massive and lethal lympho-proliferative disorder [57]. Antibody blockade of CTLA-4 induces potent anti-tumor activity through enhancing effector cells and concomitantly inhibiting T regulatory activity [58].

Given that this inhibition is not tumor-specific it is not surprising that other tumors including ovarian cancer, prostate cancer, and renal cell cancer have demonstrated durable remissions [59].

In a recent phase III trial, patients with melanoma refractory to chemotherapy or IL-2 who received ipilimumab had improved overall survival compared to those receiving the gp100 peptide vaccine, and on this basis received FDA approval in 2011 [60].

Ipilimumab holds an FDA indication for the treatment of unresectable or metastatic melanoma,with NCCN guidelines that largely elucidate specific contexts consistent with this approval including use as single agent for unresectable stage III in-transit metastases, local/satellite and/or in-transit unresectable recurrence, incompletely resected nodal recurrence, limited recurrence or metastatic disease, and disseminated recurrence or metastatic disease in patients with good performance status.

Based upon its mechanism of unleashing the immune recognition and effector system there was rationale to test the interactive effects with tumor specific antigen. Specifically, the melanoma antigen, gp100, overexpressed on this tumor and among the antigens presented in the appropriate genetic major histocompatibility complex (MHC) context (HLA*A201) represented a prime vaccine candidate. In a phase III randomized trial increased response rates were seen when vaccine was added to IL-2 compared to IL-2 alone (16% versus 6%, P=0.03); progression free survival was also significantly improved with a trend toward improved overall survival [61]. Questions arose, nonetheless, whether gp100 vaccine was an appropriate control in the aforementioned phase III trial for ipilimumab. Another phase III randomized clinical trial treating previously untreated patients with metastatic melanoma compared ipilimumab (every 3 weeks for four doses followed by `maintenance' every three months) with and without dacarbazine as the standard control; improved OS was seen including a difference at 3 years of nearly 21% vs. 12% [62].

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