VIEWPOINT

Monoclonal Antibodies in Cancer Therapy: Mechanisms, Successes and Limitations

A Coulson, A Levy, M Gossell-Williams

ABSTRACT

Rituximab was the first chemotherapeutic monoclonal antibody (CmAb) approved for clinical use in cancer therapeutics in 1997 and has significantly improved the clinical outcomes in non-Hodgkin's lymphoma. Since then, numerous CmAbs have been developed and approved for the treatment of various haematologic and solid human cancers. In this review, the classification, efficacy and significantly reduced toxicity of CmAbs available for use in the United States of America are presented. Finally, the limitations of CmAbs and future considerations are explored.

Keywords: Antigenic targets, cancer therapy, clinical benefits, monoclonal antibodies

Los Anticuerpos Monoclonales en el Tratamiento del Cáncer: Mecanismos, Éxitos y Limitaciones

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RESUMEN

Rituximab fue el primer anticuerpo monoclonal quimioterapéutico (CmAb, siglas en inglés) aprobado para uso clínico en la terapia del cáncer en 1997, y ha mejorado significativamente los resultados clínicos en el linfoma no hodgkiniano. Desde entonces, numerosos CmAbs han sido elaborados y aprobados para el tratamiento de varios cánceres humanos sólidos y hematológicos. En esta revisión, se presentan la clasificación, la eficacia y la toxicidad significativamente reducida de los CmAbs disponibles para su uso en los Estados Unidos de América. Finalmente, se exploran las limitaciones de los CmAbs y futuras consideraciones.

Palabras claves: Objetivos antigénicos, terapia del cáncer, beneficios clínicos, anticuerpos monoclonales

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INTRODUCTION

Kohler and Milstein (1) revolutionized anti-cancer therapeutics in the late 19th century with the development of hybridoma technology, now used to produce monoclonal antibodies. Since then, chemotherapeutic monoclonal antibodies (CmAbs) have emerged as standard therapeutic agents for many haematological and solid cancers in humans in the last decade. Cancer cells share many similarities with the normal host cells and this presents a challenge for achieving high levels of selective cytotoxicity. Chemotherapeutic monoclonal antibodies were engineered with the predicted advantage of specificity, thus acting as 'targeting missiles' toward cancer cells (2).

Classification of chemotherapeutic monoclonal antibodies

Advances in genetic engineering techniques have resulted in the development of four main types of CmAbs: murine, chimeric, humanized and human CmAbs. Murine CmAbs, derived exclusively from mouse, were the first to be applied

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in cancer chemotherapeutics. Utilization, however, was rapidly revoked because of inability to effectively interact with components of the human immune system due to their foreign nature and subsequent limited recognition by the host immune system. Chimeric CmAbs typically comprise variable regions derived from a murine source and constant regions (65%) derived from a human source (3). Chimeric CmAbs can also be non-humanized (chimeric trifunctional CmAbs), rat-mouse hybrid monoclonal antibodies that have three different antigen-binding specificities: for tumour cells, T lymphocyte cells and one for accessory cells (4). The development of chimeric CmAbs that possess a fully human Fc portion provided considerably less immunogenic and more efficient interaction with human effector cells and the complement system than murine CmAbs (5). Humanized CmAbs are predominantly (90%) engineered from a human source with the exception that the complementarity-determining regions of the Fab portion are of murine origin; they are even less immunogenic than chimeric CmAbs. Human CmAbs, which are 100% human, are engineered from transgenic mice, and compared to chimeric and humanized CmAbs, have higher affinity values toward human antigens and minimal or no hypersensitivity responses (6).

Chemotherapeutic monoclonal antibodies may be conjugated to other forms of cancer therapy and this facilitates greater efficacy. More importantly, conjugation provides targeted attack at cancer cells and therefore reduced widespread systemic toxicities to normal cells. There are three types of conjugated CmAbs: radiolabelled CmAbs which are linked to radionuclide particles (7), chemolabelled CmAbs which are attached to anti-neoplastic drugs (8) and immunotoxin CmAbs which are attached to plant and bacterial toxins (9). Table 1 lists the CmAbs approved by the United States of America (USA) Food and Drug Administration (FDA) for use in oncology by type and year approved.

Table 1: Unconjugated and conjugated monoclonal antibodies currently approved by the Food and Drug Administration (FDA) for cancer therapy

CmAb	**Type**	**Year approved**
	Unconjugated	
Rituximab	Chimeric IgG1	1997
Trastuzumab	Humanized IgG1	1998
Alemtuzumab	Humanized IgG1	2001
Tositumomab	Murine IgG2a	2003
Cetuximab	Chimeric IgG1	2004
Bevacizumab	Humanized IgG1	2004
Panitumumab	Human IgG2	2006
Catumaxomab*	Chimeric mouse-rat hybrid	2009
Ofatumumab	Human IgG1	2009
Ipilimumab	Human IgG1	2011
Pertuzumab	Humanized IgG1	2012
Denosumab	Human IgG2	2013
	Conjugated	
Ibritumomab tiuxetan	Murine IgG1	
	Radionucleotide (Yttrium^{90} or Indium^{111})	2002
Tositumomab	Murine IgG2a	
	Radionucleotide (Iodine^{131})	2003
Brentuximab vedotin	Chimeric IgG1	
	Drug (Auristatin E)	2011
Trastuzumab emtansine	Humanized IgG1	
	Drug (Mertansine)	2013

*Approved by European Medicines Agencies and undergoing trials in the USA. CmAb: chemotherapeutic monoclonal antibody. Source: 10, 37

Mechanisms of action of CmAbs: a targeted approach with a promising future

Chemotherapeutic monoclonal antibodies target cancer cells by binding to cell surface antigens. Cell surface antigens include antigens associated with growth and differentiation, such as cluster of differentiation (CD; *eg* CD20, CD 30, CD 33 and CD52), carcino-embryonic antigen (CEA), epidermal growth factor receptor (EGFR), receptor activator of nuclear factor kappa-B ligand (RANKL), human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), integrins (*eg* αVβ3 and α5β1), fibroblast activation protein (FAP) and extracellular matrix metalloproteinase inducers [EMMPRIN] (10–13). Once CmAbs attach to the specific target antigen tumour, cell destruction is effected through three main mechanisms:

- direct tumour cell death by mechanisms such as targeting and inhibition of cell survival signalling, the induction of apoptosis or through the direct delivery of cytotoxic drugs or radioisotope modalities by conjugated antibodies (14–16).
- immune mediated tumour cell killing by engaging antibody-dependent-cell-mediated-cytotoxicity, complement-mediated-cytotoxicity and activating cellular phagocytosis (4, 17, 18). Additionally, immunostimulatory CmAbs can activate T lymphocyte cells through the inhibition of T lymphocyte inhibitory receptors (19).
- vascular ablation and disruption of stromal interaction with cancer cells. This denies tumours of blood supply and supporting network promotes tumour regression (20).

Clinical successes

Table 2 lists FDA approved CmAbs for haematologic and solid cancers. Among the most noteworthy candidates for haematologic tumours are rituximab, alemtuzumab and ofatumumab, brentuximab vedotin, ^{131}I-tositumomab and ^{90}Y-iIbritumomab tiuxetan. Rituximab was the first CmAb approved for clinical use in cancer therapeutics and has proven to be highly effective in increasing the overall survival rates in lymphoproliferative disorders. In a study involving 48 patients with chronic or small lymphocytic leukaemia, rituximab therapy resulted in an overall response rate of 58%, with 9% complete responses (21). Similar suc-

Table 2: Antigenic targets, cancer indication and mechanism of action (MOA) of the chemotherapeutic monoclonal antibodies (CmAbs) currently approved by the Food and Drug Administration (FDA) for cancer therapy

CmAb	Antigenic target	MOA	Main cancer indication(s)
Rituximab	CD20	ADCC, CMC, induces apoptosis	Non-Hodgkin's lymphoma
Alemtuzumab	CD52	Induces apoptosis, CMC, ADCC	Chronic lymphocytic leukaemia
Tositumomab	CD20	ADCC, induces apoptosis	Non-Hodgkin's lymphoma
Cetuximab	EGFR	ADCC, inhibition of EGFR signalling	Colorectal cancer, head and neck cancer
Bevacizumab	VEGF	Inhibition of VEGF signalling	Lung cancer, renal cancer, colorectal cancer, brain cancer, breast cancer
Panitumumab	EGFR	Inhibition of EGFR signalling	Colorectal cancer
Catumaxomab*	EpCAM	ADCC, T-cell mediated lysis, phagocytosis *via* FcγR accessory cells	Malignant ascites in patients with EpCAM $^{+}$ve cancers
Ofatumumab	CD20	ADCC, CMC	Chronic lymphocytic leukaemia
Denosumab	RANKL	Inhibition of RANKL signalling	Breast cancer, prostate cancer
Ipilimumab	CTLA-4		Melanoma
Pertuzumab	HER2	Inhibition of HER2 signalling	Breast cancer
^{90}Y-ibritumomab tiuxetan	CD20	Radioisotope (^{90}-Yttrium) delivery	Non-Hodgkin's lymphoma
^{131}-I tositumomab	CD20	Radioisotope (^{131}-Iodine) delivery	Non-Hodgkin's lymphoma
Brentuximab vedotin	CD30	Cytotoxic drug (auristatin E) delivery	Hodgkin's lymphoma, anaplastic large cell lymphoma
Trastuzumab emtansine	HER2	Inhibition of HER2 signalling, ADCC	Breast cancer

*Approved by European Medicines Agency and undergoing trials in the USA.
Source: 10, 37–40

cess has been reported for treatment of follicular lymphoma (22) and diffuse large B-cell lymphoma (23). Brentuximab vedotin is indicated in Hodgkin's lymphoma and anaplastic large cell lymphoma where it has produced a response rate of greater than 50% in both malignancies and achieved 57% remission in patients with anaplastic large cell lymphoma (24). ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan are indicated for treatment of relapsed or refractory low-grade non-Hodgkin's lymphoma and have achieved high response rates (25).

Trastuzumab, cetuximab, panitumumab, bevacizumab, catumaxomab, ipilimumab and denosumab are FDA approved for use across several solid cancers. Trastuzumab emtansine selectively targets HER2; in a clinical trial involving 137 patients with HER2-positive breast cancer, trastuzumab proved to significantly improve progressive-free survival time (14.2 months) compared to 9.2 months with the conventional chemotherapeutic agent, docetaxel (26). The clinical improvement in response rate, progression-free survival and overall survival of bevacizumab in non-small cell lung cancer were confirmed in a recent meta-analysis which included 15 650 patients collected from 30 randomized clinical trials (27).

Limitations and promising future

Compared with conventional chemotherapy, the adverse effects of unconjugated CmAbs are usually mild, while conjugated CmAbs precipitate severe adverse effects (3). These adverse effects are commonly related to the antigens they target and the intravenous route of administration. For example, bevacizumab targets tumour blood vessel growth and causes adverse effects such as hypertension and kidney damage (28). More than 90% of patients on rituximab therapy experience infusion-related reactions such as cytokine release syndrome and tumour lysis syndrome (23). Intravenous administration of alemtuzumab is associated with lymphopenia and concomitant immunosuppression (29). Conjugated agents such as brentuximab vedotin precipitate cumulative peripheral neuropathy (30) while myelosuppression is the main toxicity of ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan (31). Other adverse effects common to most CmAbs are chills, weakness, headache, nausea, vomiting, diarrhoea, hypotension and rashes.

Although great strides have been made in antibody engineering and cancer therapy, production cost is estimated at twice that required for conventional drugs (32). Production requires the use of very large cultures of cells, which are expensive to maintain, primarily as a consequence of high turnover of disposables, such as media, and the continuous requirement for sophisticated purification steps to ensure clinical quality (33). Thus, the cost to the users is restrictive. In 2012, the calculated per patient cost of treatment of colorectal cancer with CmAbs (bevacizumab, cetuximab and panitumumab) was US$30 400 in comparison to US$17 500 for the use of conventional chemotherapeutic drugs [oxaliplatin, irinotecan, fluorouracil and leucovorin] (34).

Moreover, while the introduction of substitutes (generics) for innovator brands of small drug molecules provides cost savings of 80% to USA medical expense, no such benefit occurs with the biological substitutes (biosimilars), where the savings amounts to 30% at best (35, 36).

There is no debating that the engineering of CmAbs signified a key milestone in cancer therapeutics, and with the success rate of bringing these drugs to the market being better than that of small molecular drugs, it is expected that pharmaceutical companies will continue to progress toward more specific, less toxic and more cost-effective CmAbs.

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