Biochemical Pharmacology 79 (2010) 1544–1552

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Emerging immunotherapies targeting CD30 in Hodgkin's lymphoma

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ARTICLE INFO

Article history:
Received 6 November 2009
Accepted 14 January 2010

Keywords:
Cancer
Tumor necrosis factor (TNF)
Hodgkin's lymphoma (HL)
Anaplastic large cell lymphomas (ALCL)
Hematologic malignancies
Lymphoproliferative diseases
Reed–Sternberg cells
Antibody–drug conjugates
Immunotoxins
Immune evasion

ABSTRACT

The immunotherapy of Hodgkin's lymphoma (HL) has been particularly challenging because of the unique features of tumor intrinsic and host mediated factors, interfering with the antitumor activities of therapeutic antibodies. Despite a wide array of compounds tested successfully in preclinical studies, immunotherapy in HL patients resulted in only limited success when compared to the significant improvements in patient survival provided by chemotherapeutic agents. Antibody–drug conjugates (ADCs) may surmount the restrictions posed by the unique pathobiology of HL tumors as they combine the selective tumor targeting of monoclonal antibodies with the potent anti-neoplastic activities of cytotoxic drugs. In early clinical trials, this class of compounds induced robust antitumor effects in patients with relapsed or refractory lymphoproliferative diseases, in the absence of overt toxicities, while naked antibodies failed to induce therapeutic benefit. Here we review some of the unique features of HL tumor biology and the key advantages of ADC-based lymphoma therapies, which may ultimately account for the improved therapeutic benefit provided by ADCs compared to first generation immunotherapeutics tested in HL patients.

1. Introduction

There are an estimated 8000 new Hodgkin's lymphoma (HL) cases diagnosed annually in the United States and Canada. Advances made in the use of combined chemotherapy and radiotherapy in HL over the past half-century resulted in durable remission rates of approximately 80%. However, these multi-agent regimens confer a significant morbidity such as secondary malignancies and infertility. Furthermore, between 20% and 30% of patients with HL will be refractory to initial therapy and will relapse after initial treatment. Overall, effective therapeutic modalities for refractory or relapsed patients are limited and most carry a high morbidity rate. Thus, there continues to be an unmet medical need for this group of patients with a poor prognosis, providing a strong rationale for the development of novel therapies with improved safety and/or efficacy profiles.

Naked antibodies have the potential to lyse tumor cells *via* Fc-mediated effector mechanisms such as antibody-dependent cellular cytotoxicity (ADCC) and were developed successfully in hematologic malignancies. Based on their presence on HL tumors, a large number of cell surface proteins such as CD20, CD30, IL13 receptor, CD40, RANK ligand and DR4 are being considered for potential targets for antibody-based immunotherapy for HL. Several antibodies targeting the above receptors are being developed in HL and are at various stages of preclinical and clinical testing (reviewed in ref. [1]). However, most of the antibodies that advanced to the clinic, including anti-CD20 and anti-CD30 antibodies, displayed only limited efficacy when administered as a single agent to HL patients ([2–4] and Table 1).

To improve on the efficacy of naked antibodies, a variety of approaches targeting HL tumor cells are being considered. For example, technologies to enhance the antitumor activities of naked antibodies, such as radioimmunoconjugates, antibody–cytokine and –toxin conjugates as well as bi-specific antibodies are being developed [5]. In general, these antibody derivatives display superior activities compared to naked antibodies when tested in preclinical and clinical studies. However, a prevalence of anti-therapeutic antibodies (ATA) in patients treated with the first generation of murine antibody-based drug conjugates, limited the utility of this approach for prolonged treatment of HL (Table 1) [6]. Immunoconjugates also pose an additional level of complexity based on the differences in the sensitivity of their target cells towards the various classes of cytotoxics employed, ultimately affecting their therapeutic indexes.

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doi:10.1016/j.bcp.2010.01.015

Table 1
CD30 directed immunotherapy in clinical development.

Year, reference	Drug	Sponsor	Study type	*N*	CR + PR	Comments
1992, [79]	Murine anti-CD30-saporin conjugate (Ber-H2/SO6)		Pilot	4	75%	100% ATA
1997, [86]	Murine anti-CD16/CD30		Phase I/II	15	13%	60% ATA
2001, [85]	Murine anti-CD16/30 combined with IL2, GM-CSF		Pilot	16	25%	38% ATA
2002, [87]	Anti-CD64/CD30		Phase I	10	40%	80% ATA
2002, [94]	Murine anti-CD30-ricin-A conjugate (Ki-4.dgA)		Phase I	17	7%	41% ATA
2005, [88]	Murine anti-CD30-^{131}iodine-conjugate		Phase I	22	27%	18% ATA delayed grade 4 cytopenia in 32%
2002, [88]	Chimerized anti-CD30 mAb (cAC10, SGN-30)	Seattle Genetics	Phase I	13	15%	1–15 mg/kg
2003, [67]	cAC10, SGN-30	Seattle Genetics	Phase I	24	4%	2–12 mg/kg
2004, [3]	cAC10, SGN-30	Seatlle Genetics/NCI	Phase II	35	0%	6 mg/kg, qwkx6
2004, [74]	Humanized anti-CD30-mAb (parental 5F11, MDX-060)	Medarex	Phase I/II	72	8%	Qwkx4
2008, [90]	cAC10-auristatin conjugate (cAC10-vcMMAE, SGN-35)	Seattle Genetics	Phase I	39	45%	0% ATA 1.2–2.7 mg/kg, qwkx $\geq$2
2005, [73]	Humanized, effector cell enhanced anti-CD30 mAb (cAC10, AmAb^{TM} 2513)	Xencor	Phase I initiated in 2008			
2007, [75]	Humanized, effector cell enhanced anti-CD30 mAb (parental MDC-060, MDX-1401)	Medarex	Phase II	72	8%	1–15 mg/kg, qwkx4

This table is modified from ref. [6].
There has been a significant increase in the response rate of HL and ALL patients treated with immunotoxin conjugates such as SGN-35, when compared to unarmed antibodies (i.e. SGN-30, MDX-1401 and AmAb^{TM} 2513). The success of the first generation immunoconjugates targeting HL was limited due to the high incidence of ATA: anti-therapeutic antibodies.

To circumvent these limitations, recent clinical trials in Hodgkin's lymphoma employed humanized antibodies or humanized radioimmuno-antibody conjugates, targeting cell surface antigens expressed on HL tumors. In addition, virus specific antigens were targeted by adoptive immunotherapy or vaccine strategies (reviewed in refs. [6,7]) and novel small molecule inhibitors are being developed in HL indications (reviewed in ref. [8]). In this review, we summarize the preclinical and clinical progress made with naked antibodies and antibody–drug conjugates targeting tumor antigens expressed in HL. The main focus is directed towards compounds targeting the CD30 antigen and the response rates reported from early stage clinical trials (Table 1). We also highlight challenges posed by the unique pathobiology of HL (Table 2) and discuss potential ways to overcome some of these limitations by developing the next generation of immunotherapeutics for the treatment of HL patients.

2. Hodgkin's lymphoma, a challenging disease for immunotherapy

A variety of unique biological feature present in HL and summarized in Table 2, may limited the efficacy of first generation biotherapeutics developed for the treatment of HL (summarized in Table 1). Global immunosuppression has long been known to be associated with HL and several mechanisms employed by the tumor itself leading to immunosuppression, were identified previously. Most of the tumor mass in classical HL is comprised of a benign, dense inflammatory infiltrate consisting of B cells, CD4+ T cells, eosinophils, neutrophils, monocytes and macrophages (Fig. 1), surrounding the malignant Hodgkin–Reed–Sternberg (HRS) cells and that is enriched in inhibitory T-regulatory cells [9]. T-regulatory cells induce a profoundly immunosuppressive environment, by targeting effector cell

Table 2
Unique pathobiological features of HL and potential mitigation by therapeutic compounds.

HL pathobiology	Mechanism	Indications	Mitigation	References
Alterations in signaling pathways affecting cell survival	NF-κB activation	HL (RSC), NHL	mAbs/ADCs interfering with NF-κB, combination with NF-κB pathway inhibitors	[35]
	Inhibition of intrinsic and extrinsic apoptotic pathways, alterations in cFLIP, XIAP, BclX_L expression	HL (RSC)	ADCs, combination with targeted compounds activating apoptotic pathways	[36–38]
	MAP/ERK activation	HL (RSC)	ADCs, combination treatment with MAPK inhibitors	[40]
	AP-1 expression	HL, ALCL		[41]
	PI3-K/AKT activity	HL (RSC)	ADCs, combination with PI3-K inhibitors	[42]
Immune evasion	Inhibitory T-regulatory cells	HL	ADCs, chemo combo	[9]
	Th2-type T-cell response	HL (RSC)	ADCs, chemo combo	[95]
	Resistance to CD95	HL (RSC)	siRNA to cFLIP	[12]
	Expression of FAS ligand, RCAS1	HL (RSC)	ADCs	[96,97]
Resistance to chemotherapy	Bcl-2	HL (RSC), NHL	Certain ADCs/mAbs inducing chemo-sensitization, combination anti-Bcl-2 compounds	[98]
Low frequency of RSC, high numbers of inflammatory infiltrates	Insufficient drug delivery	HL	ADCs with bystander activity, combination with cytoreductive agents	[91–93]
Changes in extracellular matrix, solid tumor like appearance	Increased survival of neoplastic cells, pro-angiogenic environment	HL	ADCs, cytoreductive therapy, combination with anti-angiogenic compounds	[15]
Pro-angiogenic environment	Pro-angiogenic cytokine secretion	HL	Combination with anti-angiogenic compounds, chemotherapy	[99]
Low mitotic index of HRS cells	Long G1 phase and expression of abnormally stable cyclin E	HL (RSC)	Prolonged exposure to cytotoxic drugs, including ADCs, mAbs	[13]

A variety of unique biological features of HL may have contributed for the dismal efficacy observed for various biotherapeutic compounds tested in HL and ALL patients. Antibody–drug conjugates may be able to overcome these limitations, as their efficacy is less affected by immune evasion mechanisms, alterations in signaling pathways within HRS cells or changes in the angiogenic phenotype of tumors.