Journal of Controlled Release 286 (2018) 154–166

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review article

The potential for clinical translation of antibody-targeted nanoparticles in the treatment of acute myeloid leukaemia

Jianfeng Guo[a,*], Xue Luan[a], Zhongcheng Cong[a], Yao Sun[a], Limei Wang[a,b], Sharon L. McKenna[c], Mary R. Cahill[d], Caitriona M. O'Driscoll[e,**]

[a] School of Pharmaceutical Sciences, Jilin University, Changchun 130021, China
[b] The General Hospital of FAW, Changchun 130011, China
[c] Cork Cancer Research Centre, University College Cork, Ireland
[d] Department of Haematology, Cork University Hospital, Ireland
[e] Pharmacodelivery Group, School of Pharmacy, University College Cork, Cork, Ireland

ARTICLE INFO

Keywords:
Non-viral delivery vectors
Leukaemia-associated antigens
Bone marrow microenvironment
Translational research

ABSTRACT

Acute myeloid leukaemia (AML) is a heterogeneous haematopoietic malignancy. Currently, treatment options offer a 5 year survival of < 60%. In elderly patients, where the incidence is highest, the survival is much lower. Current standard treatments have significant toxicity and are least well tolerated in older adults, where the need is greatest. Therefore, alternatives are required. Monoclonal antibodies (mAbs), due to the specific targeting to cell surface proteins (i.e. antigens), represent a promising strategy for drug delivery to malignant cells. This concept favours the therapeutic ratio simultaneously by reducing toxicity and increasing efficacy. Although delivery of chemotherapeutics, genes and imaging agents using multifunctional nanoparticles has been substantially explored in treating solid cancers, less information on this approach is available in the case of AML. This review describes the development of antibody-targeted nanoparticulate drug delivery systems, and discusses the barriers to clinical translation in the treatment of AML.

1. Introduction

Acute myeloid leukaemia (AML) is a heterogeneous haematopoietic malignancy characterised by the abnormal proliferation of immature white blood cells. These cells expand in the bone marrow (BM) and spread to the peripheral blood and other tissues (e.g. the spleen and liver) via the blood circulation. AML causes a variety of symptoms mostly as a result of bone marrow failure. These include anaemia, bleeding, and an increased risk of life-threatening infections. The incidence of AML in developed countries is increasing with an aging population; for instance, new cases and deaths were estimated at 19,520 and 10,670 respectively in the United States in 2018 [1]. In addition, though rare, AML accounts for up to 20% of childhood leukaemia with a 5-year survival of < 40% [2]. This contrasts to the > 90% survival in childhood acute lymphocytic leukaemia (ALL). AML patients face a poor prognosis and high mortality rates, therefore, improved therapeutic approaches are urgently required.

The application of chemotherapeutics with or without the transplantation of multipotent haematopoietic stem cells (HSCs) that come from a donor is still the mainstay of medical treatment for AML [except AML subtype M3, according to the FAB (French-American-British) classification system] [3]. In addition to leukaemia cells, cytotoxic drugs also act on healthy tissues causing unwanted side-effects such as mucositis, cardiotoxicity, hepatotoxicity and multifactorial immune damage resulting in opportunistic infections. Therefore, alternative and adjunctive treatment strategies designed to improve outcomes particularly for the elderly, children and those in poor prognosis categories represent an unmet clinical need.

1.1. Monoclonal antibodies

One rationale to improve therapeutic efficacy and lower toxicity of chemotherapeutics is to conjugate them to antibodies (mostly monoclonal antibodies, mAbs) achieving antibody drug conjugates (ADCs). Antibodies or antibody derivatives can specifically recognise the tumour antigen on the plasma membrane and therefore target the delivery of cytotoxic drugs towards tumour tissues [4].

In addition to targeting specificity, mAbs, once bound to the tumour

* Correspondence to: Jianfeng Guo, School of Pharmaceutical Sciences, Jilin University, Changchun 130021, China.
** Correspondence to: Caitriona O'Driscoll, School of Pharmacy, University College Cork, Cork, Ireland.
E-mail addresses: jguo@jlu.edu.cn (J. Guo), caitriona.odriscoll@ucc.ie (C.M. O'Driscoll).

https://doi.org/10.1016/j.jconrel.2018.07.024
Received 28 April 2018; Received in revised form 12 July 2018; Accepted 13 July 2018

cells, can also effectuate anti-cancer activities via antibody-mediated immune-reactivity [5]. As a result, a combination of the cytotoxic activity of chemotherapeutic drugs and the immunotherapeutic function of mAbs may achieve a synergistic therapeutic effect, providing a promising anti-cancer strategy for clinical application [6].

The drug-to-antibody ratio (DAR), which is the average number of therapeutic agents conjugated to antibodies, is known to significantly affect the therapeutic results of ADCs [7]. A low DAR value impacts negatively on the anti-cancer potential, while a high DAR value may cause aggregation, lower pharmacokinetics, and induce non-specific toxicity. The DAR value is generally ~ 3.5 to 4 achieved with current conjugation chemistry (i.e. cysteine inter-chain disulphide bond reduction or lysine side-chain amidation) [7]; however, this low amount of drugs delivered by mAbs into cancer cells may cause clinical failure of ADCs containing conventional cytotoxic drugs [8]. In contrast, the high drug loading efficiency which can be achieved using a NP-based delivery approach represents a significant formulation advantage compared to ADCs. Development of nanotechnology for therapeutic agents in the treatment of AML will be discussed in Sections 1.3 and 2.2.

1.2. Antigens as selective cellular markers for AML delivery

The advancements of antigen-specific immunotherapeutic approaches such as ADCs and mAb-mediated immunotherapy are highly dependent on the choice of the target antigens [9], [10]. Antigens considered appropriate as selective cellular markers for AML delivery should be: 1) AML-specific, expressed in leukaemia cells as well as leukaemia stem cells (LSCs); 2) essential for the phenotypes (e.g. the development, maintenance, and/or progression of AML); 3) highly internalised into cells (see discussion in Sections 2.2.4); and 4) clinically relevant. These features of AML-associated antigens have been substantially reviewed in [11]. With recent advances in exploiting the human immune system for control or even eradication of AML, a variety of cell surface and transmembrane proteins expressed on AML cells and LSCs have recently been identified [11].

1.2.1. CD33

CD33 is a well-known therapeutic target for AML as it is broadly identified on adult and childhood AML cells but rarely found in the normal haematopoiesis [12]. When bound by antibodies, CD33 has strong endocytic capacity that can achieve the internalisation of the antibody/antigen complex [13].

Gemtuzumab ozogamicin (GO) is a humanised anti-CD33 mAb conjugated with a toxin called calicheamicin (it causes DNA degradation) [14]. Improved therapeutic responses were achieved using GO in a specific subset of AML patients (i.e. adults older than 60 years with first relapse and not considered for other chemotherapeutic drugs) [15]. Despite receiving accelerated approval by the U.S. FDA in 2000, this medicine was withdrawn in 2010 from use in the U.S. due to toxicity issues [12]. Nevertheless, as CD33 is still a promising target for both paediatric and adult AML, GO has recently been reused for the treatment of AML in the U.S. market [16]. In addition, novel anti-CD33 therapeutic strategies are currently being investigated for patients with various subtypes of AML (reviewed in [13]).

1.2.2. CD123

CD123 [also known as the interleukin-3 receptor α-chain (IL-3Rα)], plays a key role in cell cycle, differentiation, and apoptosis of early haematopoietic cells [17]. The overexpression of CD123 has been identified on human AML cells and LSCs, indicating a promising role for anti-CD123 immunotherapeutic treatment [18], [19], [20].

Indeed, Jin et al. demonstrated that an anti-CD123 mAb (7G3) could successfully reduce the AML burden in mice xenografted using primary cells from patients with CD123-positive AML [18]. This anti-AML effect was due to two activities: 1) the growth of leukaemia cells was inhibited by 7G3-mediated suppression of the IL-3-associated signalling pathways and 2) 7G3 induced innate immunity (natural killer cells and/or $CD122^+$-dependent cells), both of which collectively inhibited the homing and growth of primary cells in vivo and as a result significantly improved the survival of xenografted mice [18]. In addition, a novel ADC comprising the CD123-specific antibody conjugated to *Pseudomonas exotoxin A* (SL-101) was developed by Han and colleagues, and the therapeutic effects of SL-101 and the underlying mechanisms of the anti-leukaemia function were studied in vitro and in vivo [19]. The mechanistic studies showed that the cytotoxic activities of SL-101 were due to the efficient internalisation of the antibody, activation of apoptotic progression, and blockage of p-STAT5 and p-AKT signalling pathways [19]. As a result, the engraftment capacity of primary cells pretreated with SL-101 was significantly impaired in a xenograft mouse model when compared to untreated counterparts.

1.2.3. CD44

CD44, known to be expressed in many mammalian cell types, plays a key role in the proliferation, differentiation and migration of cells [21], [22]. CD44 is known as one of the stem cell markers, first identified for HSCs and subsequently confirmed for cancer stem cells (CSCs) and LSCs [21], [22]. One of CD44 ligands is hyaluronic acid [an extracellular matrix (ECM) component], and the interaction between hyaluronic acid and CD44 mediates the adhesion and migration of LSCs to the stroma in the BM [23]. Recently, CD44 has been validated as a promising target for development of anti-CD44 immunotherapeutics in the treatment of AML [24], [25].

It was reported by Jin and co-workers that the administration of a CD44-specific mAb (H90) to mice 10 days after transplantation of primary AML LSCs significantly reduced the leukaemia burden and inhibited the AML engraftment in comparison to the control IgG [24]. In contrast, H90 could not affect the homing capacity of normal cord blood or BM $CD34^+$ cells, illustrating the specificity of the antibody effect for AML [24]. In addition, a recombinant anti-CD44 humanised mAb (RG7356) that can inhibit the interaction between CD44 and hyaluronic acid, has recently been investigated for patients with relapsed/refractory AML [25]. The clinical results indicated that although this medicine was well tolerated, it lacked clinical activity as a monotherapy. The favourable safety profiles, however, support further investigation of RG7356 as a combination therapy with chemotherapeutics [25].

1.2.4. CD47

CD47, a transmembrane protein belonging to the Ig superfamily, is associated with the proliferation, adhesion, migration and apoptosis of cells [26], [27]. The dysregulation of CD47 causes the evasion of anticancer immunity [28]. The highly expressed CD47 has been identified on AML LSCs versus normal HSCs, and the increased CD47 expression was correlated with a deteriorating overall survival in AML patients [29], suggesting the potential of CD47 as an immunotherapeutic biomarker for AML [30], [31].

It is well established that the interaction between CD47 and signal regulatory protein-α (SIRPα, expressed on innate immune cells) can impair the phagocytosis of malignant cells by macrophages [28]. Majeti et al. therefore developed anti-CD47 mAbs to disrupt the CD47-SIRPα interaction [29]; as a result, these mAbs preferentially induced phagocytosis of LSCs and inhibited the leukaemia engraftment in vivo, without showing significant toxicity. In addition, a humanised CD44-specific mAb (Hu5F9-G4) has recently been developed to promote anti-AML immunity [31]. In this study, Hu5F9-G4 successfully activated phagocytosis of leukaemia cells and cured the disease in vivo, achieving long-term survival of mice xenografted with patient samples. Moreover, toxicokinetic data from non-human primates indicated that Hu5F9-G4 could be safely administrated at doses capable of resulting in potentially therapeutic functions [31]. As a result, this mAb is now undergoing Phase 1 trials for AML (NCT02216409).