Dependence of the anti-CD66 antibody biodistribution on the dissociation constant: A simulation study

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Abstract

In radioimmunotherapy (RIT) with radiolabelled anti-CD66 antibody, the red bone marrow is selectively irradiated. A preceding study, employing a physiologically based pharmacokinetic model, has shown that currently about 50% of the anti-CD66 antibody is accumulated in the red marrow. In this work, the potential improvement of the biodistribution is quantified for other anti-CD66 antibodies with lower dissociation constants K_D. Biodistribution simulations were performed based on a recently published mathematical model for a 10- and 100-fold lower monovalent K_D. The therapeutic index was compared to the therapeutic index which is achieved using the actual antibody. The simulations indicate that a considerably increased therapeutic index can be obtained by decreasing the dissociation constant. A reduction of the K_D to 10-fold or 100-fold lower values would lead to an improvement of the therapeutic index, by a factor of 2.4-5 and 2.4-6.5 respectively. To investigate the predicted improvement of the radioimmunotherapy, new anti-CD66 antibodies with lower dissociation constants should be developed.

Bioverteilung von Anti-CD66-Antikörpern in Abhängigkeit von der Dissoziationskonstanten: Eine Simulationsstudie

Zusammenfassung

Bei der Radioimmuntherapie mit radiomarkierten Anti-CD66-Antikörpern wird das rote Knochenmark selektiv bestrahlt. Eine vorangehende Studie, bei der ein physiologisch basiertes pharmakokinetisches Modell eingesetzt wurde, zeigte eine Anreicherung des Anti-CD66-Antikörpers von ca. 50% im roten Knochenmark. In dieser Arbeit wird die potentielle Verbesserung der Bioverteilung durch die Verwendung von Antikörpern mit geringeren Dissoziationskonstanten K_D untersucht. Basierend auf einem kürzlich veröffentlichten Modell wurden Bioverteilungssimulationen mit 10- und 100-fach niedrigerem monovalenten K_D durchgeführt. Der therapeutische Index, hier definiert als das Verhältnis der Verweildauern von rotem Knochenmark und Leber,

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wurde mit dem therapeutischen Index des tatsächlich eingesetzten Antikörpers verglichen. Die Simulationen deuten darauf hin, dass ein deutlich größerer therapeutischer Index mit niedrigeren Dissoziationskonstanten erreicht werden kann. Eine Verringerung des K_D-Wertes um das 10- und 100-fache führt zu einem um den Faktor 2,4-5 beziehungsweise 2,4-6,5 größeren therapeutischen Index. Um diese vorhergesagte Verbesserung der Radioimmuntherapie zu untersuchen, sollten neue anti-CD66-Antikörper mit niedrigeren Dissoziationskonstanten entwickelt werden.

Keywords: radioimmunotherapy, anti-CD66 antibody, model simulations, dissociation constant, therapeutic index

Schlüsselwörter: Radioimmuntherapie, Anti-CD66-Antikörper, Modell-Simulationen, Dissoziationskonstante, therapeutischer Index

1 Introduction

Radioimmunotherapy (RIT) with ^{90}Y-labelled anti-CD66 antibody is used to selectively deliver radiation to the red bone marrow [1–3]. Pretherapeutic measurements of the ^{111}In-labelled anti-CD66 antibody biodistribution have shown that about 50% of the antibody accumulates in the red bone marrow [4]. The modelling of RIT with anti-CD66 antibody indicates a potential improvement using smaller amounts of antibody for therapy [4]. A further approach to increase the red marrow uptake of the labelled antibody might be using an antibody directed against the same antigen with a lower dissociation constant K_D. Thomas et al. have demonstrated using computer simulations that (for the proper antibody dose and antigen distribution) a decreasing K_D leads to a higher therapeutic index, i.e. a higher ratio of absorbed doses in solid tumour versus normal tissue [5]. Thus, the development of a novel antibody with a reduced dissociation constant might increase the therapeutic index and therefore enhance the effectiveness and efficiency of the therapy.

Here, the benefit of a novel anti-CD66 antibody with a lower K_D was quantified. Computer simulations were conducted using a recently published anti-CD66 antibody physiologically based pharmacokinetic (PBPK) model [4]. The ratios of the residence times for the red marrow and liver were computed for a 10- and 100-fold lower monovalent K_D and the potential improvement compared to the currently used antibody were calculated.

2 Methods

To investigate the influence of a lower K_D in RIT with anti-CD66 antibody on the biodistribution, a physiologically based pharmacokinetic model [6,7] was employed [4]. The recently developed model includes four major antigen expressing sites (red marrow, spleen, liver and blood), association and dissociation of antibody antigen complexes, degradation and excretion of bound and unbound antibody, blood volumes and blood flows to the specific organs. Monovalent and bivalent binding is explicitly incorporated [8]. The model parameters were fitted to measured biodistribution data of 8 patients. Here, the published model and the estimated parameters are utilized [4]. The biodistribution was simulated for the previously estimated monovalent $K_D = 71$ nM and for a 10- and 100-fold lower dissociation rate. In the model it is assumed that, the bivalent dissociation constant is directly proportional to the monovalent dissociation constant [4,8]. The modelling software SAAM2 [9] was used to determine the residence times of red bone marrow, spleen and liver for each K_D. The therapeutic index was defined as the ratio of the residence times of the red marrow and the liver.

3 Results

The simulations demonstrate a significant dependence of the biokinetics on the dissociation constant for the investigated anti-CD66 antibody. A typical example of fit curves for the actual K_D and the simulated biokinetics for $K_{D/10}$ and $K_{D/100}$ is depicted in Figure 1. The corresponding residence times for the accumulating organs are presented in Table 1. Setting the dissociation constants to lower values, the red marrow residence times are increased and the residence time of the liver are decreased. It can be assumed that the toxicity in highly perfused organs like the liver is reduced, as the serum level of antibody is clearing considerably faster due to a lower K_D (Figure 1). The simulations indicate that a substantial improvement of the therapeutic index can be achieved by using an antibody with a lower dissociation constant (Table 2). A 10-fold or 100-fold lower K_D would result in a therapeutic index larger by a factor of 2.4-5 and 2.4-6.5, respectively (Table 2).