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A Clearance Step will become Increasingly Crucial for Pretargeted Tumor Therapy when Tumor Accumulation is Improved

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Abstract

This is a commentary on a paper we published in Cancer Biother Radiopharm 2010. This commentary addresses related concerns about adding a separate clearing agent in the pretargeted tumor therapy. Previous investigations of tumor pretargeting mostly focused on utilizing the characteristic rapid clearance of a small therapeutic effector to limit toxicity exposure to normal tissues, but at a price of reduced tumor accumulation. Nevertheless, at least in theory, this reduction of tumor accumulation is not inevitable. The effector structure should be able to be modulated for its highest tumor accumulation while keeping the normal tissue background of the free effector negligible. However, so far little effort has been made in this area. In connection with the reduction of the toxicity to normal tissues, inclusion of a clearing step is well known. This commentary is to indicate that, in the pretargeted tumor therapy, inclusion of a clearance step will be more crucial when tumor accumulation of the effector is improved. It is the prerequisite to redeem the benefit of improved tumor accumulation.

Introduction

Pretargeting is a targeting strategy in which, an antitumor Ab is injected, followed a couple of days later by another injection of the effector. "Effector" is a term for the tumor targeting agent in a pretargeting setting. It is a small water-soluble molecule that bears a toxic payload, binds the pretargeted Ab, and is excreted very rapidly into urine if not bound to the Ab or tumor.

A few years ago, we published a paper in Cancer Biotherapy and Radiopharmaceuticals entitled "adding a clearing agent to pretargeting does not lower the tumor accumulation of the effector as predicted" [1]. At that time, there was a concern that the use of a clearing agent may reduce the tumor accumulation of the later injected small molecule effector. The paper told a story that as long as the available pretargeted binding sites for the effector are sufficient in the tumor, the percent tumor accumulation for that effector in % ID or % ID/g would be at the same value. The story is backed by a delivery theory that, in an infinite short period of time, the tumor accumulation increment of the effector is the product of the blood flow, blood concentration, the tumor trapping fraction, and the infinite small time interval [2]. Thus, the tumor accumulation of the effector that localizes in tumor with an infinite affinity is the integration of the increment over the entire period. If the pretargeted binding sites are sufficient, the tumor accumulation is at the maximum. The maximum percent tumor accumulation (MPTA) of an effector is proportional to the tumor blood flow, the area under the blood curve (AUC_{Blood}), and the tumor trapping fraction, but independent of the number of pretargeted binding sites (i.e., the number of the pretargeting Abs in the tumor). It is also independent of different pretargeting Abs used [3].

Comments

The use of a clearing agent does lower the tumor accumulation of the effector in a situation where the effector dosage over-matches the available pretargeted binding sites [4,5]. This may happen when the clearing agent competes with the effector for binding or when the effector dosage is excessive. Thus it would have been more scientifically correct if we used "MPTA" in the title instead of "tumor accumulation", but at that time MPTA was not a well-known term.

Although it is clarified that adding a clearing agent does not reduce tumor accumulation as long as the effector is not overdosed, there is another concern that inclusion of a clearing step makes the overall procedure too difficult for an ultimate translation to the clinic. The on-going clinical trials of pretargeted tumor therapy do not include a clearing agent. Most likely, this is based on a cost-effective consideration. It is true the more steps, the less likely to receive an FDA approval. Another reason is probably that currently there is not a well-established clearing agent although every pretargeting mechanism allows for using one. However, it may not be true that even if a life could be saved, FDA would not consider the 3 injections to be recommendable as a standard care procedure in the clinic. The key question is whether the 3-step pretargeted therapy would make a life-saving technology.

It is evident that cancer cells can be destroyed if using a correct toxic agent, either radio- or other toxic-therapeutics, at a sufficiently high dose as recently proved in hematological cancer therapy [6-9], but the progress of solid tumor therapy is slow. One of the major impediments is the limited blood flow that restrains the delivery of an adequate toxicity dose to solid tumors [10-11]. To deliver a higher toxicity dose, one way or another, this limited blood flow has to be circumvented.

Direct targeting strategy (direct delivery of a toxic agent by loading it onto a tumor targeting agent) is employed more often than the pretargeting strategy considered herein, but that strategy seems unlikely to succeed. So far, solid tumor eradication remains unfulfilled in the clinic [11,12]. Small water-soluble therapeutic agents accumulate in tumor rapidly but are excreted also rapidly and very often accumulate in normal tissues as well. Large targeting molecules or serum-protein-bound small molecules do not pass through the

glomerular filtration membrane easily, stay longer in the circulation and do counteract the limited tumor blood flow, but the blood background would be elevated at the same time [6]. Modulation of the molecular size of a direct targeting agent to achieve the highest tumor accumulation with minimal normal tissue binding could be a solution. However, the targeting moiety in a direct targeting fashion may constrain a desired modulation.

Pretargeting strategy separates the tumor targeting of an antitumor Ab and its labeling by using the 2nd effector injection. The advantage is often described as the delayed toxicity injection eliminates the toxicity exposure to the blood and normal tissues during the phases of tumor targeting and normal tissue clearance of the Ab. Fewer researchers are working on this strategy than on the conventional direct targeting strategy, but it is encouraging that in the past several years more groups especially in Europe have joined the efforts to develop pretargeting technologies [13-15]. This strategy improves the therapeutic index as compared to the direct Ab targeting but has not achieved tumor eradication yet. The complexity in optimizing the dosage and timing is considered as a difficulty, but it may not be a real one as we have addressed this issue [16].

Another advantage of the pretargeting strategy is not well known. This strategy offers the flexibility in modulating the effector structure while keeping the normal tissue background low. After separating the injection of a pretargeting agent and its labeling, pharmacokinetic modulation of the effector is no longer constrained by the original Ab structure. The nature of pretargeting is a conversion of the native targets on the cell surface to some artificial targets for the effector. Thus, the structural modulation is now subject to the restriction of the recognition moiety, but there are multiple recognition systems to be chosen [13,17-20]. Our morpholino oligomer/c-morpholino oligomer recognition system alone, [19] for example, allows for modulating the effector molecular properties (size, charge, and affinity) without elevating the normal tissue background. Earlier, there were some systemic pharmacokinetic modulation investigations, but that was limited to lowering normal tissue background rather than improving tumor accumulation [21-23].

Almost like a virgin field, the effector size (other properties as well) as a potential limiting factor for tumor accumulation has not been explored, because pretargeting strategies are less popular as compared to the direct Ab-based therapy. Though we now understand both theoretically and empirically that the reduced tumor accumulation in a pretargeting setting arises from rapid excretion of the small effectors, [2,6,23,24] initially it was often perceived that the rapid targeting of a small effector would certainly lead to higher tumor accumulation. In reality, the rapid targeting (higher tumor trapping fraction) and the rapid excretion of the effector (smaller area under blood curve) counteract each other. Optimizing the effector size should lead to improved tumor accumulation and an optimal tumor therapeutic index.

However, when tumor accumulation is improved, another downside of pretargeting strategy will emerge. If not using a clearing agent, there will be a considerable level of residual Ab in the circulation even after a couple of days following the injection of the pretargeting Ab. In this condition, an improved tumor accumulation of the effector (% ID/g) will not improve the therapeutic index. For instance, at a given dosage of a pretargeting Ab and a given time, the number of the binding sites for the effector would be at a fixed value. With an improved tumor accumulation, saturation of these sites requires a reduced effector dosage that in turn would elevate the blood background following the formula: (blood background in % ID/g = residual Ab concentration (mole/g)/dosage of effector (mole)*100%). Therefore, the blood background will be elevated proportionally to the tumor accumulation. A clearance step would remove the blood background and therefore is the prerequisite to redeem the benefit of an effector of higher tumor accumulation. Thus, inclusion of a clearance step will be increasingly important when tumor accumulation is improved.

A longer wait prior to the effector injection may be employed as an alternative, but it is much less effective and may not be even practical when the pretargeting Ab has a higher internalizing tendency. If the use of a clearing agent helps to enable tumor eradication and there is not a simpler life-saving alternative, we believe patients would not have a complaint about 3 injections or even more. If patients can walk out of a hospital tumor-free, FDA approval should not be an issue.

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