PEGASEMP – impact on the treatment of solid tumors with a novel microenvironment targeting strategy

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Abstract

Cancer is one of the leading causes for mortality in the western civilization of the twenty-first century (WHO, 2009), with more than 1.4 million new cases and more than half a million deaths in 2008, in the United States of America (USA) [1].

In Europe, 2.9 million new cases and 1.7 million deaths were reported in 2004 [2] and, in 2007, the numbers rose to 3.2 million diagnosed cancer cases (excluding non-melanoma skin cancers) and 1.7 million deaths. Unlike hematologic cancers, such as leukemia, accessibility of current treatments to solid cancers is a major obstacle to therapeutic success. Moreover, traditional chemotherapy, upon administration in the blood stream, accumulates extensively in healthy tissues, because it lacks selectivity towards tumor cells. Side effects that occur as a result of the toxic accumulation (hair loss, immune system depression, vomiting and nausea) often lead to administration of anticancer chemotherapeutics at sub-optimal doses, resulting in failure of therapy. This is frequently accompanied by drug resistance and metastatic disease.

Targeted therapies to cancer cells, which aim at circumventing these occurrences, can be an appealing alternative, but they have specific disadvantages: (i) patients must be eligible to treatment specificities. This translates into a minor percentage of patients benefiting from therapy; (ii) targeted therapies to cancer cells do not accumulate rapidly and extensively in the tumor mass, for the reason that solid tumors are not readily accessible to therapeutic agents administered in the blood stream, and the increasing pressure gradient towards the inner core of the tumor impairs drug penetration into the compact tumor mass.

Cancer is, thus, one disease where there is still an unmet medical need and where more tumor-specific treatments are urgently required.

We have developed a nanotechnology-based platform (PEGASEMP) for the specific (targeted) delivery of a chemotherapeutic drug (doxorubicin) to the tumor microenvironment. Proof of concept was performed in an animal model of breast cancer.

PEGASEMP, has proven to accumulate rapid and preferentially in a solid tumor, unlike any other drug delivery nanoparticle.

Upon administration in the blood stream, PEGASEMP was able to specifically deliver doxorubicin to the tumor, rapidly (within just 4 h) and efficiently. The reason for this occurrence owes to the dual targeting ability of the platform. Instead of targeting only the cancer cells, PEGASEMP also targets endothelial cells from the tumor blood vessels. PEGASEMP recognizes the one receptor these two cell populations have in common. When reaching the tumor location, PEGASEMP does not depend only on extravasation from the blood stream to accumulate in the target site. The platform recognizes the target cells readily available in the tumor blood vessels and arrests immediately in the tumor site. Hence, we were able to report an accumulation of approximately 50 % the injected dose/g of tissue within only 4 h after administration in the blood stream [3]. This is a major breakthrough if we take into consideration

that others have achieved a 5%/g of tissue accumulation over 48 to 72 h when targeting cancer cells within a solid tumor [4].

Nonetheless, increased specificity is not the only advantage PEGASEMP has over other therapeutic options. The platform was engineered to enable a burst release of drug inside the target cells. This triggered release mechanism allows stability in the blood stream (low leakage of the drug from the platform throughout time) and an increased concentration of the drug reaching the tumor site and being effective only where it is necessary. Moreover, PEGASEMP provides an opportunity for using the same therapeutic agent to treat more than one type of cancer. Given the versatility of the platform, other clinical indications are being investigated for PEGASEMP. If preliminary results prove to be right, the perspective of applying one platform to tumors with diverse histological origins will increase the potential of the technology and give rise to a revolutionary anticancer therapy.

References

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