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Parameters affecting the enhanced permeability and retention effect: the need for patient selection

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Abstract: The enhanced permeability and retention (EPR) effect constitutes the rationale by which nanotechnologies selectively target drugs to tumors. Despite promising pre-clinical and clinical results, these technologies have, in our view, underachieved compared to their potential, possibly due to a suboptimal exploitation of the EPR effect. Here, we have systematically analyzed clinical data to identify key parameters affecting the extent of the EPR effect. An analysis of 17 clinical studies showed that the magnitude of the EPR effect was varied and was influenced by tumor type and size. Pancreatic, colon, breast, and stomach cancers showed the highest levels of accumulation of nanomedicines. Tumor size also had an effect on the accumulation of nanomedicines, with large size tumors having higher accumulation than both medium- and very large- sized tumors. However, medium tumors had the highest percentage of cases (100% of patients) with evidence of the EPR effect. Moreover, tumor perfusion, angiogenesis, inflammation in tumor tissues, and other factors also emerged as additional parameters that might affect the accumulation of nanomedicines into tumors. At the end of the commentary, we propose two strategies for identification of suitable patient sub-populations, with respect to the EPR effect, in order to maximize therapeutic outcome.

Keywords: cancer; targeted drug delivery; prodrugs; nanotechnology; pharmacokinetics;

INTRODUCTION

In the 1980s, Maeda and his group reported for the first time that a polymer-protein conjugate (a conjugate of styrene maleic anhydride and neocarzinostatin, SMANCS) accumulated preferentially in tumors[1]. They attributed this phenomenon to the combination of increased extravasation (enhanced

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