Hydroxypropyl-Acrylamide Polymer-Conjugated Pirarubicin (P-THP)

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Hydroxypropyl methacrylate (HPMA) polymer-conjugated pirarubicin (P-THP), an innovative polymer-conjugated anticancer drug, has highly tumor-specific distribution owing to the enhanced permeability and retention (EPR) effect. The tumor-targeting EPR effect of macromolecules was originally described in solid tumors by Matsumura and Maeda (a coauthor of the present article) in 1986. The aberrant architecture of tumorous blood vessels, active production of various vascular permeability factors, and lack of lymphatic drainage in tumor tissue, constitute the tumor-specific conditions necessary for the EPR effect.

Keywords: enhanced permeability and retention effect ; EPR effect ; hydroxypropyl acrylamide polymer-conjugated pirarubicin ; P-THP ; anthracyclines ; nanomedicine ; drug delivery system ; DDS ; targeted drug delivery ; pediatric cancers

1. Introduction

The maximum effectiveness with minimum toxicity describes the ideal anti-cancer drug. Recent developments in cancer genetics and molecular biology have accelerated the development of therapeutics away from cytotoxic agents to molecular targeting agents. The number of late-stage pipeline therapies has grown from 481 in 2008 to 849 in 2018 for a total increase of 77%. In contrast, only 62 (7.3%) cytotoxic agents were being developed in 2018 [1]. However, conventional cytotoxic agents, such as alkylating agents and anthracyclines, are still the mainstay of multidisciplinary treatment for pediatric cancers even in the era of precision medicine [2]. In this regard, improving the drug-delivery system (DDS) for cytotoxic agents can help reducing their toxicity and enable increased dose intensity. Therefore, further research and development of more effective DDS are warranted.

Hydroxypropyl methacrylate (HPMA) polymer-conjugated pirarubicin (P-THP), an innovative polymer-conjugated anticancer drug, has highly tumor-specific distribution owing to the enhanced permeability and retention (EPR) effect [3][4]. The tumor-targeting EPR effect of macromolecules was originally described in solid tumors by Matsumura and Maeda (a coauthor of the present article) in 1986 [5]. The aberrant architecture of tumorous blood vessels, active production of various vascular permeability factors, and lack of lymphatic drainage in tumor tissue, constitute the tumor-specific conditions necessary for the EPR effect [3][5]. Although, the mechanism of P-THP is often confused with that of other nanomedicine agents, liposomal doxorubicin (Doxil ® ; Janssen Pharmaceuticals, Beerse, Belgium) [6], which has been approved for clinical use in several nations, and possesses distinct pharmacodynamic characteristics that set it apart from liposomal doxorubicin. In the present review, the authors explain the mechanism underlying the high tumor-selectivity of P-THP and the application of this agent to a wide variety of pediatric malignancies.

2. EPR Effect and Its Mechanism

To confirm the MW dependency of the EPR effect, biocompatible synthetic copolymers of HPMA, which can be synthesized to have various MW ranging from 4.5 to 800 kDa, were used. Repetition of the experiment described above using S-180 bearing mice with intravenous administration of radioiodinated HPMA found that the EPR effect occurred only when molecules with MW > 40 kDa were used. Although all the HPMA copolymers accumulated in the tumor regardless of MW (1.0–1.5% of the injected dose per gram of tumor) within ten minutes after injection, only copolymers with MW > 40 kDa showed significantly higher intratumor accumulation after six hours [7]. Blood clearance was slower with high MW copolymers, and the tissue levels were consistently 3–5% dose/gm kidney in the early phase, but their accumulation in the kidneys and liver was not time-dependent [7]. The EPR effect in solid tumors appeared to arise primarily from the difference in clearance rates between the solid tumors and the normal tissues after the initial penetration of the polymers into these tissues.

Evidence of the EPR effect in clinical practice can be observed via angiography of liver tumors using a lipid contrast agent (Lipiodol ® ; Guerbet LLC, Princeton, NJ, USA) administered intraarterially [8] and via gallium scintigraphy using radioactive gallium-transferrin complex (90 kDa), which accumulates in tumors and is therefore useful for their diagnosis [9]. As discussed later in this article, the EPR effect is advantageous not only for diagnosis, but also for therapy because of this preferential retention of macromolecular drugs.

The EPR effect reflects several, unique, vascular properties in tumor tissue having anatomical, physiological, and biochemical aspects.

Last, tumor-associated lymphatic vessels also show irregularities in structure, with some tumors showing a complete lack of lymphatics. Drainage has therefore been found to be impaired in tumors [5][7][10], contributing to prolonged drug retention within the tumors.

3. Design of Tumor-Specific Drug Delivery Utilizing the EPR Effects

There are several requirements in designing a nanoparticle meeting the first criterion. As a minimal requirement, there should be no interaction with blood components or blood vessels, no antigenicity, no clearance by the reticuloendothelial system, and no cell lysis. Only when these conditions are satisfied can the next three factors be considered.

First, a sufficient concentration of the nanoparticle needs to be maintained in the blood stream for several hours to exert the EPR effect, resulting in selective accumulation of the drug in the tumor [7][11]. The stability of the nanoparticle is necessary for maintaining a sufficient half-life. Most non-covalently connected micelles (NCCMs) are very unstable in the blood stream; block copolymer micelle carriers containing doxorubicin, such as NK911 (Nippon Kayaku Co., Ltd.; Tokyo, Japan), for instance, have a very short plasma half-life (t 1/2) of less than three hours in humans, which is thought to be the reasons for its ineffectiveness [12][13].

Second, the nanoparticles must be larger than 40 kDa to prevent their excretion via the kidneys. HPMA polymer-conjugated doxorubicin, which is very similar in design to P-THP, failed to produce a good antitumor effect in past studies [14] probably because, among other possible reasons, the HPMA polymer was too small (20–30 kDa) to produce the EPR effect.

To design a nanoparticle which is capable of releasing the APIs into the tumor tissue, tumor-specific conditions may be exploited to cleave the bond connecting the APIs to the particle. One possibility is using a peptide-linker cleavable by cathepsin B, which is highly expressed in various tumor cells [15]. Another possibility is using acid-cleavable linkages, such as the hydrazone-bond, which was used with P-THP, as will be shown in the following sections.

4. Proposed Clinical Development of P-THP for Pediatric Solid Tumors

As multiagent cytotoxic chemotherapy is still the mainstay of multidisciplinary treatments for pediatric cancers, the potential role of P-THP depends on the disease. Multiple factors, including cancer subtypes, stage, disease status (e.g., newly diagnosed or refractory/recurrent), and comorbidities, must be accounted for when developing the optimal treatment strategy for each cancer subtype. Strategic considerations in P-THP development, summarized in **Table 1** , will be discussed in the following sections.

Table 1. Clinical development of P-THP for pediatric solid tumors.

Phase	Disease/Status	Primary Aim	Design
1	Miscellaneous/recurrent Cohort 1 (h/o anthracyclines +) Cohort 2 (h/o anthracyclines −)	To determine MTD and safety profile of P-THP monotherapy	Rolling-six dose-escalation
1–2	Miscellaneous/recurrent	To determine MTD and safety profile of combination therapy containing P-THP	Rolling-six dose-escalation plus extension cohort
2	Non-rhabdomyosarcoma STS	Safety/efficacy evaluation of P-THP monotherapy	1-arm, exploratory
	Miscellaneous/newly diagnosed	Safety/efficacy evaluation of combination therapy	wP2 design, etc.

Phase	Disease/Status	Primary Aim	Design
3	Miscellaneous/recurrent	Efficacy confirmation of P-THP monotherapy	RCT w/ BSC
	Hepatoblastoma, Wilms Tumor, etc.	Superiority confirmation of P-THP replacement	RCT w/dox regimen
	Osteosarcoma, Ewing sarcoma	Superiority confirmation of P-THP regimen (possibly w/intensification of anthracycline)	RCT w/dox regimen
	Neuroblastoma, Rhabdomyosarcoma	Superiority confirmation of P-THP add-on	RCT w/std regimen

BSC; best supportive care, h/o; history of, MTD; maximal tolerating dose, P-THP; hydroxypropyl acrylamide polymer-conjugated pirarubicin, RCT; randomized controlled trial, STS; soft tissue sarcoma, w/; with, wP2; window phase 2.

Cardiovascular comorbidity secondary to anthracycline treatment may affect the survival outcome in pediatric cancers. A clinical trial of AML found that both event-free survival (hazard ratio: 1.6; p = 0.004) and overall survival (hazard ratio: 1.6, p = 0.005) were significantly worse in patients with cardiotoxicity [16]. Although dexrazoxane, a cardioprotective agent, significantly reduced the incidence of cardiovascular complications in cancer patients, it carries the risk of toxicities, including secondary malignancy [17]. From a safety point-of-view, replacing conventional anthracyclines with P-THP, which is at least equally effective theoretically while having fewer toxicities because of its selective distribution in the tumor site, may yield better efficacy outcomes due to the lower risk of adverse effects, including cardiotoxicity.

The role of anthracyclines in neuroblastoma, which still has a poor prognosis, is controversial. Although anthracyclines are considered a part of standard regimens for high-risk neuroblastoma in the US and Japan, doxorubicin use is avoided in first-line chemotherapy regimens containing cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide (rapid COJEC) in the EU [18]. The reason for this avoidance derives from a study by Shafford, et al., which found no improvement in the treatment response rate in neuroblastoma after the addition of doxorubicin every three weeks to induction chemotherapy with vincristine, cisplatin, epipodophyllotoxin (VM26), and cyclophosphamide (OPEC) [19].

In these studies, the additional toxicities of doxorubicin, such as cytopenia and mucositis, might have delayed the subsequent treatment course and increased adverse events affecting the clinical outcomes. The effectiveness of adding anthracycline (i.e., P-THP) to the current standard regimen in improving clinical outcomes in neuroblastoma and rhabdomyosarcoma should also be tested.

References

1. Global Oncology Trends 2019. Therapeutics, Clinical Development and Health System Implications. Institute Report (30 May 2019). Available online: https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2019 (accessed on 5 April 2021).
2. Fox, E.; Blaney, S.M.; Moreno, L.; Norris, R.; Skolnic, J.M.; Adamson, P.C.; Balis, F.M. General principles of chemotherapy. In Pizzo and Poplack's Pediatric Oncology, 8th ed.; Blaney, S.M., Adamson, P.C., Helman, L.J., Eds.; Wolters Kluwer: New York, NY, USA, 2020; pp. 239–302.
3. Maeda, H. The 35th Anniversary of the Discovery of EPR Effect: A New Wave of Nanomedicines for Tumor-Targeted Drug Delivery—Personal Remarks and Future Prospects. J. Pers. Med. 2021, 11, 229.
4. Nakamura, H.; Etrych, T.; Chytil, P.; Ohkubo, M.; Fang, J.; Ulbrich, K.; Maeda, H. Two step mechanisms of tumor selective delivery of N-(2-hydroxypropyl)methacrylamide copolymer conjugated with pirarubicin via an acid-cleavable linkage. J. Control. Release 2014, 174, 81–87.
5. Matsumura, Y.; Maeda, H. A new concept for macromolecular therapeutics in cancer chemotherapy: Mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 1986, 46, 6387–6392.
6. Gabizon, A.; Catane, R.; Uziely, B.; Kaufman, B.; Safra, T.; Cohen, R.; Martin, F.; Huang, A.; Barenholz, Y. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. Cancer Res. 1994, 54, 987–992.
7. Noguchi, Y.; Wu, J.; Duncan, R.; Strohalm, J.; Ulbrich, K.; Akaike, T.; Maeda, H. Early Phase Tumor Accumulation of Macromolecules: A Great Difference in Clearance Rate between Tumor and Normal Tissues. Jpn. J. Cancer Res. 1998, 89, 307–314.

8. Konno, T.; Maeda, H.; Iwai, K.; Maki, S.; Tashiro, S.; Uchida, M.; Miyauchi, Y. Selective targeting of anti-cancer drug an d simultaneous image enhancement in solid tumors by arterially administered lipid contrast medium. Cancer 1984, 54, 2367–2374.
9. Edwards, C.L.; Hayes, R.L. Tumor scanning with 67Ga citrate. J. Nucl. Med. 1969, 10, 103–105.
10. Iwai, K.; Maeda, H.; Konno, T. Use of oily contrast medium for selective drug targeting to tumor: Enhanced therapeutic effect and X-ray image. Cancer Res. 1984, 44, 2115–2121.
11. Seymour, L.; Miyamoto, Y.; Maeda, H.; Brereton, M.; Strohalm, J.; Ulbrich, K.; Duncan, R. Influence of molecular weight on passive tumour accumulation of a soluble macromolecular drug carrier. Eur. J. Cancer 1995, 31, 766–770.
12. Nakanishi, T.; Fukushima, S.; Okamoto, K.; Suzuki, M.; Matsumura, Y.; Yokoyama, M.; Okano, T.; Sakurai, Y.; Kataoka, K. Development of the polymer micelle carrier system for doxorubicin. J. Control. Release 2001, 74, 295–302.
13. Matsumura, Y.; Hamaguchi, T.; Ura, T.; Muro, K.; Yamada, Y.; Shimada, Y.; Shirao, K.; Okusaka, T.; Ueno, H.; Ikeda, M.; et al. Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin. Br. J. Cancer 2004, 91, 1775–1781.
14. Etrych, T.; Jelínková, M.; Říhová, B.; Ulbrich, K. New HPMA copolymers containing doxorubicin bound via pH-sensitive linkage: Synthesis and preliminary in vitro and in vivo biological properties. J. Control. Release 2001, 73, 89–102.
15. Malugin, A.; Kopečková, P.; Kopeček, J. Liberation of doxorubicin from HPMA copolymer conjugate is essential for the i nduction of cell cycle arrest and nuclear fragmentation in ovarian carcinoma cells. J. Control. Release 2007, 124, 6–10.
16. Getz, K.D.; Sung, L.; Ky, B.; Gerbing, R.B.; Leger, K.J.; Leahy, A.B.; Sack, L.; Woods, W.G.; Alonzo, T.; Gamis, A.; et al. Occurrence of Treatment-Related Cardiotoxicity and Its Impact on Outcomes among Children Treated in the AAML053 1 Clinical Trial: A Report from the Children's Oncology Group. J. Clin. Oncol. 2019, 37, 12–21.
17. Shaikh, F.; Dupuis, L.L.; Alexander, S.; Gupta, A.; Mertens, L.; Nathan, P.C. Cardioprotection and Second Malignant Ne oplasms Associated with Dexrazoxane in Children Receiving Anthracycline Chemotherapy: A Systematic Review and M eta-Analysis. J. Natl. Cancer Inst. 2015, 108, djv357.
18. Pearson, A.D.; Pinkerton, C.R.; Lewis, I.J.; Imeson, J.; Ellershaw, C.; Machin, D.; European Neuroblastoma Study Grou p; Children's Cancer and Leukaemia Group (CCLG formerly United Kingdom Children's Cancer Study Group). High-do se rapid and standard induction chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: A randomised trial. Lancet Oncol. 2008, 9, 247–256.
19. Shafford, E.A.; Rogers, D.W.; Pritchard, J. Advanced neuroblastoma: Improved response rate using a multiagent regim en (OPEC) including sequential cisplatin and VM-26. J. Clin. Oncol. 1984, 2, 742–747.
