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Commentary

Drug Delivery Systems for Intraperitoneal Therapy

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Abstract. Disorders associated with the peritoneal cavity include peritoneal adhesions and intraperitoneal (IP) malignancies. To prevent peritoneal adhesions, physical barrier devices are used to prevent organs from contacting other structures in the abdomen and forming adhesions, or pharmacological agents that interfere with adhesion formation are administered intraperitoneally. IP malignancies are other disorders confined to the peritoneal cavity, which are treated by combination of surgical removal and chemotherapy of the residual tumor. IP drug delivery helps in the regional therapy of these disorders by providing relatively high concentration and longer half-life of a drug in the peritoneal cavity. Various studies suggest that IP delivery of anti-neoplastic agents is a promising approach for malignancies in the peritoneal cavity compared to the systemic administration. However, IP drug delivery faces several challenges, such as premature clearance of a small molecular weight drug from the peritoneal cavity, lack of target specificity, and poor drug penetration into the target tissues. Previous studies have proposed the use of micro/nanoparticles and/or hydrogel-based systems for prolonging the drug residence time in the peritoneal cavity. This commentary discusses the currently used IP drug delivery systems either clinically or experimentally and the remaining challenges in IP drug delivery for future development.

KEY WORDS: hydrogels; intraperitoneal drug delivery; intraperitoneal malignancies; micro/nanoparticles; peritoneal adhesion.

OVERVIEW OF DISORDERS IN THE PERITONEAL CAVITY

Disorders commonly associated with the peritoneal cavity include peritoneal adhesions, peritonitis, and malignancies in the peritoneal cavity. Peritoneal adhesions are abnormal tissue bands formed between intra-abdominal structures that are common consequences of peritoneal surgery, trauma, or infections. These adhesions can lead to chronic pelvic and abdominal pain, infertility, and bowel obstruction, which is potentially lethal (1,2). Due to the human suffering, mortality, and associated healthcare costs, pharmacotherapy and prevention of peritoneal adhesions have gained increasing interest among physicians, scientists, and the healthcare industry. Common cancers in the peritoneal cavity include malignant epithelial tumors (e.g., ovarian cancer), and peritoneal carcinomatosis, which results from dissemination of the primary cancers of intra-abdominal and gynecological origin (3–5). In the case of ovarian cancer, median survival rates for patients with stage-IV ovarian cancer range from 16 to 21 months (6,7). Peritoneal carcinomatosis is also associated with poor prognosis with median survival rates ranging from 3 to 4 months (4). One of the most significant challenges in the management of malignancies in the peritoneal cavity is the risk of recurrence and metastasis due to the limited treatment options, which calls for more effective therapy.

PERITONEAL ADHESIONS

The pathophysiology of peritoneal adhesion formation is extensively reviewed elsewhere (8). Efforts to prevent adhesion formation include the IP application of pharmacologic agents that influence various stages in adhesion formation cascade and the placement of barrier devices to reduce contact between the injured peritoneal surfaces during healing. Pharmacological agents used to this effect are anti-inflammatory drugs, anti-coagulants, proteolytic agents, and anti-proliferative agents. Barrier devices have been tested or commercialized in various forms, such as polymer solutions, membranes, and pre-formed or *in-situ* crosslinkable hydrogels (9). The combination of pharmacological agents and barrier devices has also been employed in experimental studies, significantly improving the anti-adhesion efficacy compared to each method alone (10,11).

MALIGNANCIES IN THE PERITONEAL CAVITY AND CURRENT THERAPY

Tumors in the peritoneal cavity are difficult to detect, and cancer often persists despite surgical and other treatments. The current treatment for malignancies in the

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peritoneal cavity is to remove macroscopic tumors by cytoreductive surgery (surgical debulking) and to remove the residual microscopic tumors by chemotherapy. For example, the standard treatment of ovarian cancer is cytoreductive surgery followed by intravenous (IV) administration of a combination of platinum or taxane analogues (12–14). Recently, a growing number of preclinical and clinical studies advocate IP chemotherapy as an alternative post-operative therapy for ovarian cancer (12,15–19). In the case of peritoneal carcinomatosis, hyperthermic peri- (concurrent) and post-operative IP chemotherapy are currently used as a preferred/optional strategy (20–22). The rationale behind IP chemotherapy is the pharmacokinetic advantage, such as high concentration and longer half-life of a drug in the peritoneal cavity, which can facilitate regional treatment of the IP malignancies (23–25). IP chemotherapy has shown positive outcomes compared to IV chemotherapy. In a clinical study performed by the Gynecologic Oncology Group, median survival of the group receiving IP cisplatin for the treatment of ovarian cancer was significantly longer than the group receiving IV cisplatin (12). A recent clinical trial by Armstrong *et al.* reported that IV paclitaxel followed by IP cisplatin resulted in longer survival in patients with advanced ovarian cancer compared to IV paclitaxel followed by IV cisplatin (15). Based on results from recent clinical trials, the National Cancer Institute issued an announcement in 2006 encouraging the IP chemotherapy for patients with optimally debulked ovarian cancer (26). Nevertheless, IP chemotherapy has not yet been adopted widely in practice for the ovarian cancer treatment, and there are several challenges in IP drug delivery.

DRUG DELIVERY SYSTEMS FOR IP THERAPY

One of the challenges in IP therapy is to provide high local concentration of a drug for longer duration. The residence time of a small molecular weight drug (<20 kDa) in the peritoneal cavity may not be sufficiently long. This leads to frequent or continuous dosing and, further, to catheter-related problems, such as catheter obstruction, increased risk of infection, and bowel complications (27). Small molecular weight drugs are absorbed through the peritoneal capillaries to enter the systemic circulation (28,29). Pharmacokinetic studies in animal models show that IP-applied docetaxel or paclitaxel was cleared from the peritoneal cavity in less than 24 h (30–32).

Given that small molecular weight drugs are readily absorbed into the systemic circulation (28,29), particulate formulations and/or hydrogel-based systems have been used to control the release of a drug and to prevent rapid clearance of drugs from the peritoneal cavity in experimental approaches (9,32–34). In one of the clinical trials, Taxol® (cremophor formulation of paclitaxel) was used in the IP treatment of ovarian cancer, maintaining a relatively high IP paclitaxel concentration compared to that in plasma for 24–48 h after single injection (25,35). In contrast, paclitaxel alone was rapidly absorbed into the systemic circulation, with bioavailability approaching unity (35). The prolonged high IP concentration of paclitaxel was due to its entrapment of paclitaxel in micelles of cremophor, a polyethoxylated castor oil (32,35), which indicates that encapsulation is an effective way of extending the residence time of a drug in the peritoneal cavity. On the other hand, Taxol® was not well tolerated in patients due to the lack of tumor specificity, accompanied by side effects, such as hypersensitivity reactions and neurotoxicity (36,37).

Particles in the peritoneal cavity are known to be absorbed to the lymphatic circulation (28,32). Hirano *et al.* showed that liposomes (50–720 nm) are trafficked to the lymphatic system, in which small ones (50 nm) easily pass through the lymph nodes to reach the thoracic lymph duct, whereas larger ones (720 nm) are mostly entrapped in the lymph nodes (28). Liposomes passing the lymph nodes were not destroyed by the resident lymphocytes (28). The ultimate fate of smaller liposomes surviving the lymphatic circulation was not discussed in this study (28), but the evidence suggests that IP-administered nanoparticles (NPs) enter the systemic circulation. Kohane *et al.* have administered poly(lactic-co-glycolic acid) (PLGA) NPs (265 nm) IP and found that the majority of NPs were cleared from the peritoneal cavity in 2 days, resulting in enlarged spleen with pale color (38). Extensive histiocytosis (foamy macrophages) was seen in the spleen (and some in the liver), indicating the presence of NPs (38). This study suggests that NPs cleared from the peritoneal cavity end up in the systemic circulation after passing lymph nodes and ducts.

Partly due to this reason, recent studies comparing drug concentrations in the peritoneal cavity, plasma, and major organs after IP administration of different particle formulations concluded that microparticles, whose sizes range from 4 to 6 μm (32,33) to 47 μm (39), were an optimal formulation for IP administration. Microparticles were cleared from the peritoneal cavity relatively slowly and had a better ability to retain the drug (32,33). On the other hand, a large particle size can cause peritoneal adhesions (15,38); thus, the benefit-to-risk ratio should be carefully considered. Another effort to prevent the premature clearance of a drug or NPs includes the use of a hydrogel or a viscous polymer solution as a carrier medium (30,31,34). When used with an *in-situ* cross-linkable hydrogel as a delivery medium, NPs remained in the peritoneal cavity for the duration of the experiment (1 week) (34), in contrast to the free NPs, which rapidly disappeared in 2 days (38).

NPs are gaining particular interest for IP delivery, as they are not only useful for delivery of chemotherapeutic drugs but also for immunotherapy and gene delivery. A recent study describes that IP delivery of a gene-polymer complex, consisting of DNA-encoding diphtheria toxin suicide protein and cationic biodegradable poly(beta-amino ester) polymer, achieved significant decrease in the tumor burden in different animal models of ovarian cancer (40).

PERSPECTIVES ON FUTURE IP DRUG DELIVERY

While some of the challenges in IP drug delivery have been addressed by the use of particulate drug delivery systems and hydrogels, at least experimentally, several issues remain to be overcome, especially for IP chemotherapy. First, poor drug penetration into the tumor tissues remains a significant challenge. This penetration issue is attributed to the high interstitial fluid pressure caused by vascular hyperpermeability and the lack of functional lymphatics (41,42).

The high interstitial fluid pressure could be a significant physiological barrier for drug delivery into the tumor, especially for a drug or a drug carrier residing in the peritoneal cavity, which approaches the tumor from the periphery. Second, while it is desirable that IP treatment maintain a long local residence time, the specificity to the target tumor should also be improved, because a drug concentrated in the peritoneal cavity can be associated with pan-peritoneal toxicity. Multidrug resistance is another important problem in chemotherapy in general. Even if anti-cancer drugs are able to locate in the tumor cells, overexpression of multi-drug transporters can efflux drugs out of the cells. In this regard, it is worthwhile to revisit the previous studies that demonstrate the advantages of colloidal carriers in overcoming the multidrug resistance (43–47). These studies show that colloidal carriers like liposomes and NPs can bypass the drug efflux pumps, achieving significantly higher drug accumulation in the cells than the free drug (43,44,47). These findings further justify the consideration of colloidal carriers for the IP chemotherapy.

In summary, future efforts for ideal drug delivery systems for IP chemotherapy should take into consideration the need for tumor specificity, efficient tissue penetration, cellular uptake and intracellular residence of a drug. In addition, when a new drug delivery system is developed for IP therapy, the biocompatibility of the carrier materials should be warranted so that complications due to the tissue responses to the materials can be avoided.

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REFERENCES

1. Liakakos T, Thomakos N, Fine PM, Dervenis C, Young RL. Peritoneal adhesions: etiology, pathophysiology, and clinical significance. Recent advances in prevention and management. Dig Surg. 2001;18:260–73.
2. Tingstedt B, Andersson E, Isaksson K, Andersson R. Clinical impact of abdominal adhesions: what is the magnitude of the problem? Scand J Gastroenterol. 2008;43:255–61.
3. Davies JM, O'Neil B. Peritoneal carcinomatosis of gastrointestinal origin: natural history and treatment options. Expert Opin Investig Drugs. 2009;18:913–9.
4. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, *et al.* Peritoneal carcinomatosis from non-gynecologic malignancies. Cancer 2000;88:358–63.
5. Drecoll E, Gaertner FC, Miederer M, Blechert B, Vallon M, Muller JM, *et al.* Treatment of peritoneal carcinomatosis by targeted delivery of the radio-labeled tumor homing peptide bi-DTPA-[F3]2 into the nucleus of tumor cells. PLoS ONE. 2009;4:e5715.
6. Akahira JI, Yoshikawa H, Shimizu Y, Tsunematsu R, Hirakawa T, Kuramoto H, *et al.* Prognostic factors of stage IV epithelial ovarian cancer: a multicenter retrospective study. Gynecol Oncol. 2001;81:398–403.
7. Curtin JP, Malik R, Venkatraman ES, Barakat RR, Hoskins WJ. Stage IV ovarian cancer: impact of surgical debulking. Gynecol Oncol. 1997;64:9–12.
8. DiZerega GS. Use of adhesion prevention barriers in pelvic reconstructive and gynecologic surgery. In: diZerega GS, editor. Peritoneal surgery. New York: Springer; 2000.
9. Yeo Y, Kohane DS. Polymers in the prevention of peritoneal adhesions. Eur J Pharm Biopharm. 2008;68:57–66.
10. Yeo Y, Adil M, Bellas E, Astashkina A, Chaudhary N, Kohane DS. Prevention of peritoneal adhesions with an *in situ* cross-linkable hyaluronan hydrogel delivering budesonide. J Control Release. 2007;120:178–85.
11. Yeo Y, Bellas E, Highley CB, Langer R, Kohane DS. Peritoneal adhesion prevention with an *in situ* cross-linkable hyaluronan gel containing tissue-type plasminogen activator in a rabbit repeated-injury model. Biomaterials 2007;28:3704–13.
12. Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, *et al.* Intraperitoneal cisplatin plus intravenous cyclophosphamide *versus* intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med. 1996;335:1950–5.
13. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med. 1996;334:1–6.
14. Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, *et al.* Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2003;21:3194–200.
15. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, *et al.* Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006;354:34–43.
16. Gadducci A, Carnino F, Chiara S, Brunetti I, Tanganelli L, Romanini A, *et al.* Intraperitoneal *versus* intravenous cisplatin in combination with intravenous cyclophosphamide and epidoxorubicin in optimally cytoreduced advanced epithelial ovarian cancer: a randomized trial of the Gruppo Oncologico Nord-Ovest. Gynecol Oncol. 2000;76:157–62.
17. Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, *et al.* Phase III trial of standard-dose intravenous cisplatin plus paclitaxel *versus* moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol. 2001;19:1001–7.
18. Polyzos A, Tsavaris N, Kosmas C, Giannikos L, Katsikas M, Kalahanis N, *et al.* A comparative study of intraperitoneal carboplatin *versus* intravenous carboplatin with intravenous cyclophosphamide in both arms as initial chemotherapy for stage III ovarian cancer. Oncology 1999;56:291–6.
19. Yen MS, Juang CM, Lai CR, Chao GC, Ng HT, Yuan CC. Intraperitoneal cisplatin-based chemotherapy *vs*. intravenous cisplatin-based chemotherapy for stage III optimally cytoreduced epithelial ovarian cancer. Int J Gynaecol Obstet. 2001;72:55–60.
20. Glockzin G, Schlitt HJ, Piso P. Peritoneal carcinomatosis: patients selection, perioperative complications and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg Oncol. 2009;7:5.
21. Gonzalez-Moreno S, Ortega-Perez G, Gonzalez-Bayon L. Indications and patient selection for cytoreductive surgery and perioperative intraperitoneal chemotherapy. J Surg Oncol. 2009;100:287–92.
22. Nissan A, Stojadinovic A, Garofalo A, Esquivel J, Piso P. Evidence-based medicine in the treatment of peritoneal carcinomatosis: past, present, and future. J Surg Oncol. 2009;100:335–44.
23. Dedrick RL, Myers CE, Bungay PM, DeVita Jr VT. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep. 1978;62:1–11.
24. Markman M. Intraperitoneal drug delivery of antineoplastics. Drugs 2001;61:1057–65.
25. Markman M, Rowinsky E, Hakes T, Reichman B, Jones W, Lewis Jr JL, *et al.* Phase I trial of intraperitoneal taxol: a Gynecoloic Oncology Group study. J Clin Oncol. 1992;10:1485–91.
26. NCI clinical announcement for Intraperitoneal chemotherapy for ovarian cancer http://ctep.cancer.gov/highlights/docs/clin_annc_010506.pdf.
27. Poveda AA, Salazar RR, del Campo JJM, Mendiola CC, Cassinello JJ, Ojeda BB, *et al.* Update in the management of

ovarian and cervical carcinoma. Clin Transl Oncol. 2007;9:443–51.
28. Hirano K, Hunt CA. Lymphatic transport of liposome-encapsulated agents: effects of liposome size following intraperitoneal administration. J Pharm Sci. 1985;74:915–21.
29. Lukas G, Brindle SD, Greengard P. The route of absorption of intraperitoneally administered compounds. J Pharmacol Exp Ther. 1971;178:562–4.
30. Mohamed F, Marchettini P, Stuart OA, Sugarbaker PH. Pharmacokinetics and tissue distribution of intraperitoneal paclitaxel with different carrier solutions. Cancer Chemother Pharmacol. 2003;52:405–10.
31. Mohamed F, Stuart OA, Sugarbaker PH. Pharmacokinetics and tissue distribution of intraperitoneal docetaxel with different carrier solutions. J Surg Res. 2003;113:114–20.
32. Tsai M, Lu Z, Wang J, Yeh T-K, Wientjes M, Au J. Effects of carrier on disposition and antitumor activity of intraperitoneal paclitaxel. Pharm Res. 2007;24:1691–701.
33. Lu Z, Tsai M, Lu D, Wang J, Wientjes MG, Au JL. Tumor-penetrating microparticles for intraperitoneal therapy of ovarian cancer. J Pharmacol Exp Ther. 2008;327:673–82.
34. Yeo Y, Ito T, Bellas E, Highley CB, Marini R, Kohane DS. *In situ* cross-linkable hyaluronan hydrogels containing polymeric nanoparticles for preventing postsurgical adhesions. Ann Surg. 2007;245:819–24.
35. Gelderblom H, Verweij J, van Zomeren DM, Buijs D, Ouwens L, Nooter K, *et al.* Influence of cremophor El on the bioavailability of intraperitoneal paclitaxel. Clin Cancer Res. 2002;8:1237–41.
36. Knemeyer I, Wientjes MG, Au JL. Cremophor reduces paclitaxel penetration into bladder wall during intravesical treatment. Cancer Chemother Pharmacol. 1999;44:241–8.
37. Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, *et al.* Hypersensitivity reactions from taxol. J Clin Oncol. 1990;8:1263–8.
38. Kohane DS, Tse JY, Yeo Y, Padera R, Shubina M, Langer R. Biodegradable polymeric microspheres and nanospheres for drug delivery in the peritoneum. J Biomed Materi Res Part A. 2006;77A:351–61.
39. Tamura T, Imai J, Matsumoto A, Tanimoto M, Suzuki A, Horikiri Y, *et al.* Organ distribution of cisplatin after intraperitoneal administration of cisplatin-loaded microspheres. Eur J Pharm Biopharm. 2002;54:1–7.
40. Huang YH, Zugates GT, Peng W, Holtz D, Dunton C, Green JJ, *et al.* Nanoparticle-delivered suicide gene therapy effectively reduces ovarian tumor burden in mice. Cancer Res. 2009;69:6184–91.
41. Fukumura D, Jain RK. Tumor microvasculature and microenvironment: targets for anti-angiogenesis and normalization. Microvasc Res. 2007;74:72–84.
42. Jain RK. Delivery of molecular and cellular medicine to solid tumors. Adv Drug Deliv Rev. 2001;46:149–68.
43. Bennis S, Chapey C, Robert J, Couvreur P. Enhanced cytotoxicity of doxorubicin encapsulated in polyisohexylcyanoacrylate nanospheres against multidrug-resistant tumour cells in culture. Eur J Cancer. 1994;30:89–93.
44. Goren D, Horowitz AT, Tzemach D, Tarshish M, Zalipsky S, Gabizon A. Nuclear delivery of doxorubicin via folate-targeted liposomes with bypass of multidrug-resistance efflux pump. Clin Cancer Res. 2000;6:1949–57.
45. Michieli M, Damiani D, Ermacora A, Masolini P, Michelutti A, Michelutti T, *et al.* Liposome-encapsulated daunorubicin for PGP-related multidrug resistance. Br J Haematol. 1999;106:92–9.
46. Rahman A, Husain SR, Siddiqui J, Verma M, Agresti M, Center M, *et al.* Liposome-mediated modulation of multidrug resistance in human HL-60 leukemia cells. J Natl Cancer Inst. 1992;84:1909–15.
47. Sadava D, Coleman A, Kane SF. Liposomal daunorubicin overcomes drug resistance in human breast, ovarian and lung carcinoma cells. J Liposome Res. 2002;12:301–9.