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Cancer Drug Resistance

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From drug potency to delivery timing: sequential local chemo-immunotherapy in colorectal peritoneal metastases

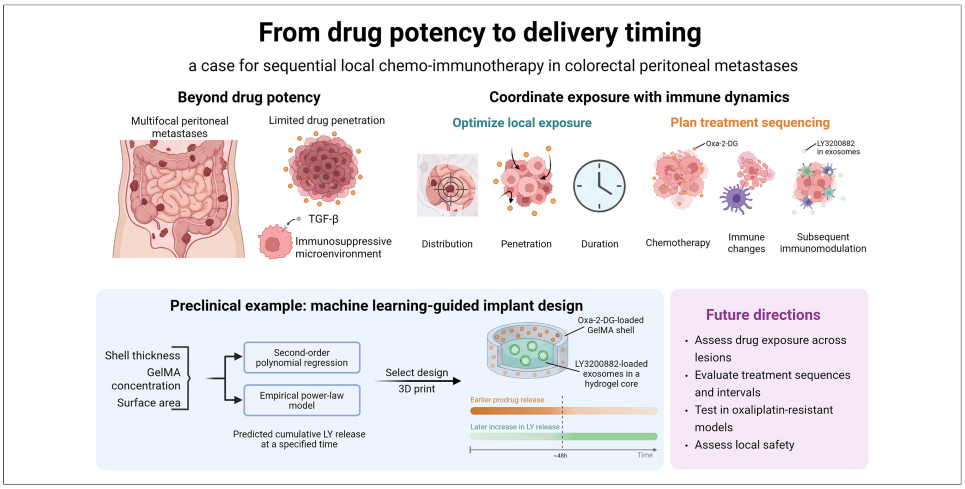
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Abstract

Treatment resistance in colorectal peritoneal metastases involves tumor-cell-intrinsic mechanisms and is compounded by dispersed lesions, limited drug penetration, and local immunosuppression. Intraperitoneal administration can increase local drug exposure, but high concentrations in peritoneal fluid do not ensure adequate delivery to all lesions. Chemotherapy-induced immune changes also make the order and timing of combination therapy important. Using our recently reported bilayer implant as an example and drawing on related local delivery studies, this commentary examines how drug exposure and treatment timing can help coordinate chemotherapy with immunomodulation. The implant, designed with machine-learning assistance and fabricated by three-dimensional (3D) printing, sequentially delivers a reduction-responsive oxaliplatin prodrug and a transforming growth factor-β (TGF-β) pathway inhibitor. It achieved greater antitumor efficacy than concurrent administration in a mouse model of peritoneal metastasis, providing experimental support for integrating prodrug activation with sequential delivery. Clinical translation will require assessment of drug distribution, release profiles, and local

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safety in relation to patients' disease characteristics, together with strategies for integrating local delivery with surgery and systemic therapy.

Major mechanisms of cancer drug resistance include target mutations, signaling pathway reactivation, clonal selection, and cellular plasticity[1]. Developing or optimizing drugs to address these mechanisms remains an important approach to overcoming resistance. Systemic treatment of colorectal peritoneal metastases includes fluoropyrimidine-based chemotherapy with oxaliplatin or irinotecan, as well as targeted therapies or immunotherapy for selected patients; cytoreductive surgery may be considered in carefully selected cases[2]. For these systemic drug therapies, however, molecular potency alone cannot ensure efficacy: drugs must reach lesions and maintain adequate intratumoral concentrations for a sufficient duration. Vascular compression by solid stress, elevated interstitial fluid pressure, extracellular matrix densification, and increased collagen cross-linking (chemical links between collagen molecules) can restrict drug transport into deeper tumor regions[3,4]. Multifocal dissemination makes it difficult to achieve adequate drug exposure across colorectal peritoneal lesions[5,6]. Molecular profiling of peritoneal metastases from patients identified the mesenchymal consensus molecular subtype of colorectal cancer [consensus molecular subtype 4 (CMS4)] as a common subtype[7]. CMS4 is characterized by enhanced transforming growth factor-β (TGF-β)-related signaling and stromal infiltration; the CMS classification also includes CMS1 (microsatellite instability–immune), CMS2 (canonical), and CMS3 (metabolic)[8]. Another study combining transcriptomic and spatial analyses found greater enrichment of TGF-β-related gene expression signatures in peritoneal metastases than in primary tumors[9]. It also identified distinct stromal phenotypes, including a fibrocollagenous phenotype with cellular and gene expression profiles associated with immunosuppression[9]. These findings suggest that treatment efficacy depends not only on cancer-cell sensitivity but also on drug access to lesions and the local immunosuppressive microenvironment. Treatment design should therefore address intratumoral distribution, sustained exposure, and treatment-induced local changes when determining the timing and sequence of subsequent interventions.

Pharmacokinetic studies showed that some drugs achieve higher concentrations in the peritoneal cavity than in plasma, providing a rationale for intraperitoneal treatment of small, poorly vascularized peritoneal lesions[6]. High peritoneal fluid concentrations nevertheless do not ensure adequate intratumoral exposure[10]. Tissue barriers still limit inward transport, potentially leaving the deeper regions of larger lesions inadequately exposed[6]. Complex abdominal anatomy and postoperative adhesions can also impede fluid distribution and contact with individual lesions[6]. Local depots, including hydrogels, can extend exposure by slowing release and prolonging retention[11]. For example, a thermosensitive hydrogel co-delivering oxaliplatin and the immune adjuvant R848 combined sustained delivery with immunomodulation in a model of diffuse colorectal peritoneal metastases[12]. These findings support evaluating both drug exposure and immune effects when assessing local delivery strategies.

Treatment-induced immune changes also provide a rationale for sequencing combination therapy. Beyond direct cytotoxicity, oxaliplatin can induce immunogenic cell death, promoting calreticulin exposure and high-mobility group box 1 (HMGB1) release to support antitumor immune priming[13]. The sequence and interval between chemotherapy and immunotherapy may therefore influence efficacy. A mouse study compared concurrent administration of a docetaxel nanoformulation and programmed cell death protein 1 (PD-1) blockade with sequential administration in either order. Docetaxel followed two days later by an anti-PD-1 antibody produced greater antitumor effects and more favorable immune-cell profiles in the models examined; the authors also related these findings to the treatments' exposure kinetics at tumor sites[14]. These results support deliberate sequencing, but the appropriate sequence and interval for other combinations should be determined from intralesional exposure and immune changes induced by the preceding treatment.

To address inadequate local exposure and limited control over the sequence of combination treatments, we developed a local sequential delivery system, as reported in *Advanced Materials*[15]. We selected an oxaliplatin prodrug and LY3200882 (LY) for their complementary actions. Oxaliplatin kills tumor cells and can induce immunogenic cell death to support immune priming[13]. LY is a selective small-molecule inhibitor of TGF-β receptor I in early clinical development, with published phase I data for oral administration[16]. It inhibits TGF-β signaling mediated by SMAD proteins, a family of intracellular signal transducers, reducing immunosuppression and changes associated with epithelial–mesenchymal transition (EMT)[15]. This choice of target is also consistent with the TGF-β-related expression profiles reported in patient lesions[9]. The reduction-responsive platinum(IV) prodrug Oxa-2-DG was used to enable reduction-triggered release of active oxaliplatin[15]. Previous research suggests that certain platinum(IV) prodrugs may reduce extracellular drug inactivation and associated resistance[17]. In CT26 cells treated for 24 h under hypoxic conditions (1% O_2), Oxa-2-DG was more cytotoxic than free oxaliplatin[15]. The proposed sequence was to initiate tumor-cell killing and immunogenic cell death with chemotherapy, then inhibit TGF-β signaling to alleviate local immunosuppression and support the ensuing antitumor immune response.

To control the timing of drug delivery, we combined machine learning with three-dimensional (3D) printing to construct a bilayer implant. The outer layer was an Oxa-2-DG-loaded gelatin methacryloyl (GelMA) hydrogel (OG). The inner layer (LEH) consisted of a thermosensitive hydrogel containing LY3200882-loaded exosomes. Compared with the injectable, *in situ*-forming hydrogel described above, the preformed implant requires intraperitoneal placement but allows the shell geometry to be predefined and the two drug-loaded components to be separated, delaying core exposure[12,15]. As the shell degrades, the outer-layer prodrug is gradually released and the core becomes progressively exposed. Both layers sustain release of their respective payloads.

The approximately 48-h target for core exposure was informed by the time course of antigen presentation and initial T-cell priming. The design also considered whether the decline in plasma concentrations of the chemotherapy drug after the initial peak might reduce cytotoxic or suppressive effects on newly activated T cells. Using data from 72 experimental samples, the study compared ten regression models to predict the cumulative fraction of LY released at a fixed time point from shell thickness, GelMA concentration, and surface area. Second-order polynomial regression and an empirical power-law model were selected for their accuracy and robustness with the small dataset. Their predictions guided the screening of parameter combinations against the target release fraction, followed by 3D printing and experimental validation. *In vitro* release experiments in 0.02% collagenase showed earlier release of the outer-layer payload and a more rapid rise in cumulative LY release after approximately 48 h[15]. The optimal interval still requires *in vivo* evaluation in relation to the drug combination, tumor characteristics, and treatment-induced microenvironmental changes.

The exosomes were derived from mitoxantrone-treated CT26 cells. When tested without LY loading, they induced calreticulin- and HMGB1-associated changes in cell assays, suggesting a potential contribution to immune priming. Fluorescence tracing showed stronger tumor signals with dye-labeled, LY-loaded exosomes than with free dye; *ex vivo* imaging at 72 h also showed strong tumor signals in the hydrogel-encapsulated group. These observations support tumor accumulation and *in vivo* retention of the labeled formulations[15]. In a mouse model of peritoneal metastasis, the bilayer implant reduced tumor burden and ascites and prolonged survival relative to concurrent administration of the two drug-loaded hydrogels (OG + LEH)[15]. Mechanistic analyses showed lower levels of phosphorylated SMAD2/3 (pSMAD2/3) in tumor tissue, consistent with reduced TGF-β signaling. Lower N-cadherin and higher E-cadherin levels were consistent with reduced EMT. Changes in immune markers and cytokines also suggested less immunosuppression[15]. Both regimens used sustained-release hydrogels, and the comparison supports the

overall therapeutic advantage of the bilayer sequential delivery strategy. Whether it improves responses in oxaliplatin-resistant tumors remains to be tested in resistant models.

Sustained or sequential local delivery is also being explored at other tumor sites. After melanoma resection, one implant preferentially released the stimulator of interferon genes (STING) agonist MSA-2 while delaying doxorubicin release[18]; implants in glioblastoma resection cavities sustained delivery of immunomodulatory small molecules[19]. Whereas a resection cavity is spatially confined, peritoneal metastases can involve multiple sites. Drug exposure must therefore also be assessed in lesions elsewhere in the peritoneal cavity.

Clinical translation also requires patient selection and integration with surgery and systemic therapy. In the multicenter randomized phase III PRODIGE 7 trial, adding short-duration, high-dose oxaliplatin-based hyperthermic intraperitoneal chemotherapy to cytoreductive surgery and systemic therapy did not improve overall survival and was associated with a higher incidence of grade ≥ 3 adverse events assessed 60 days after surgery[20]. The benefits of individual intraperitoneal regimens therefore require separate evaluation.

Future studies in oxaliplatin-resistant models could test whether reduction-responsive prodrugs and sequential immunomodulation improve tumor responses to treatment, using controls to distinguish the contributions of the prodrug, immunomodulation, and treatment sequence. For sustained sequential delivery, lesion distribution and residual tumor burden should inform studies of whether effective exposure is maintained across lesions. Different sequences and intervals should also be evaluated in relation to immune changes during treatment. Machine-learning-assisted design and 3D printing offer a means of adapting release to these requirements[15]. Patient-to-patient differences in intraperitoneal material degradation and drug distribution may affect reproducibility. Translational studies should assess whether intended release profiles are achieved and whether implantation affects postoperative recovery or increases local complications. Addressing these questions could guide patient-specific delivery regimens before clinical studies determine whether they improve disease control and survival with acceptable safety.

DECLARATIONS

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Authors' contributions

Literature review and drafting of the manuscript: Li S
Critical revision of the manuscript: Sun T
Topic development and academic supervision: Jiang C
All authors have read and approved the final manuscript.

Availability of data and materials

Not applicable.

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During the preparation of this manuscript, the AI tool Codex (OpenAI; model version GPT-6 Astra, released 2026-09-03) was used to assist with English translation, language editing, and formatting. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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