Nanomaterial-mediated platinum drug-based combinatorial cancer therapy

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Abstract
Platinum (Pt)-based drugs represent some of the most successful anticancer agents in the clinic, and they have greatly accelerated the development of cancer chemotherapy. The therapeutic efficacy of platinum drugs, however, is limited by their various side effects and the development of drug resistance by cancer cells. To address these limitations, platinum drugs are combined with other therapeutic agents as a first-line therapy for several types of cancer, and these treatments have achieved inspiring therapeutic outcomes. In some cases, however, such combinatorial treatments are inefficacious, due to the severe side effects, the short circulation half-lives, and the different pharmacokinetic properties of the combined drugs. The rapid development of nanotechnology brings opportunities to surmount these limitations. Coloading platinum drugs and other anticancer agents into nanoparticles not only increases their synergistic efficacy but also improves their pharmacokinetic properties, tumor-targeting efficiency, and other attributes that are favorable for cancer treatment. In this review, we summarize the recent developments in the application of nanotechnology for combinatorial therapy involving platinum drugs, with a focus on the design, anticancer efficacy, and other advantages of nanoparticles combining platinum drugs and other bioactive moieties. We also discuss the current challenges of these approaches and the prospects for their further development. Our summary and outlook will assist researchers to generate new ideas for the development of highly potent anticancer nanomedicine containing Pt-based drugs.

KEYWORDS
Cisplatin, combinatorial therapy, drug delivery, drug resistance, platinum drugs

1 | INTRODUCTION

The development of platinum (Pt)-based drugs was a milestone in anticancer drug development and greatly enhanced the application of chemotherapy. Pt-based drugs have been used with great success in the treatment of several types of cancers, such as lung, ovarian, head and neck, bladder, and testicular cancers.¹ The therapeutic outcome...
of Pt drugs, however, is limited by various side effects and the drug resistance developed by cancer cells. To circumvent these problems, researchers have developed various strategies including the combination of Pt drugs with other therapeutic agents, such as chemotherapeutic drugs, photodynamic therapy (PDT) agents, photothermal therapy (PTT) agents, or immune checkpoint inhibitors. Each of these combinatorial treatment strategies has its own advantages, such as improved therapeutic outcomes, a capacity to overcome drug resistance, reduced toxicity, or the ability to generate an enhanced immune response. Consequently, therapeutic successes have been achieved by the use of such strategies for the treatment of several types of cancer, such as ovarian, lung, and breast cancers. Challenges remain, however, as novel side effects and limited synergies may result from the different pharmacokinetic properties of the combined drugs. In addition, small-molecule drugs may have short circulation times, a lack of tumor selectivity, and be subject to premature activation outside of cancer cells. Therefore, the synergies between combined agents and their tumor-specific delivery must be optimized to realize their therapeutic potential.

Nanomaterials have proven to be ideal platforms for drug delivery, and there is extensive evidence for the improved pharmacokinetic properties of drugs loaded on nanomaterials. For example, several types of nanoparticles, such as drug-loaded liposomes, have been approved as clinical treatments, and are therapeutically superior to the corresponding free drugs. As delivery vehicles for combinatorial therapy, nanoparticles synchronously release the combined drugs at the desired site to increase the synergistic effects, and can be flexibly tailored to have other properties that are favorable for cancer treatment, such as tumor-targeting ability, controllable drug-release properties, improved bioavailability, increased circulation half-life, and the ability to overcome biological barriers. As a result, lots of studies have been carried out to develop nanomaterial-based drug-delivery platforms to realize improved therapy using Pt-based drugs combined with other therapeutic agents.

Choosing appropriate Pt drugs is important for the design of nanotherapeutic systems. Although Pt-based anticancer drugs are well known as DNA damaging agents with a broad spectrum of anticancer activity, each Pt drug has its unique features. For example, cisplatin is especially effective toward testicular cancer, carboplatin has more moderate toxicity than other Pt drugs, and oxaliplatin is preferred for colorectal cancer treatment. Besides conventional Pt(II) drugs, kinetic inert Pt(IV) prodrugs are also suitable loading cargos for nanomaterials. Compared with Pt(II) drugs, inert Pt(IV) prodrugs are of low biological activities, whereas upon certain stimulating factors, for example, reducing agents in cancer cells, Pt(IV) prodrugs can be reduced to Pt(II) active forms to kill cancer cells. The two extra axial ligands enable Pt(IV) prodrugs to be functionalized with more properties, such as controllable activation or enhanced compatibility with nanomaterials. Several Pt(IV) prodrugs including c.c,t-[diaminedichlorodisuccinatoplatinum(IV)] (DSCP), diazide-Pt(IV), and diiodido-Pt(IV) have been loaded in nanomaterials for cancer treatment (Figure 1). Consequently, the broad-spectrum anticancer activity and flexible modification property of Pt complexes ensure their great applicability for different nanodelivery systems.

In this review, we summarize the recent developments and achievements in the application of combinatorial therapies using nanomaterial-based drug delivery systems that combine platinum chemotherapy with other chemotherapy, PDT, PTT, or immunotherapy. We focus on the design, anticancer activities, and other advantages of nanodelivery systems over conventional drug combinatorial therapy. Finally, we outline the current challenges and perspectives of nanomaterial-mediated Pt drug-based combinatorial anticancer therapy.

2 | NANOMATERIALS TO REALIZE COTREATMENT OF MULTICHEMOTHERAPEUTIC REGIMENS CONTAINING PLATINUM DRUGS

Chemotherapy remains an effective mode of cancer treatment. Many “cocktails” of Pt-based drugs and other mechanistically complementary chemotherapy drugs are a mainstay in the clinic. Such cotreatment strategies can overcome the drug resistance of cancer cells and reduce the required dose of each drug, thereby minimizing the dose-dependent side effects of chemotherapeutics. Combinatorial drug treatment has shown improved therapeutic outcomes for several types of cancer, but the anticancer efficacy of this approach is limited by the different pharmacokinetic properties of the combined drugs. Therefore, there is great interest in the development of nanomaterials as carriers that can deliver drug combinations to cancer cells, and thus enhance drug synergies and improve the therapeutic utility of combinatorial treatments.

2.1 | Co-delivery of Pt drugs with topoisomerase inhibitors

Topoisomerase (TOP) inhibitors are chemical agents that block the function of topoisomerase, the enzyme that controls DNA overwinding or underwinding. Inhibition of topoisomerase can suppress the ability of DNA repair
and sensitize cancer cells to Pt-induced DNA damage. Importantly, DNA damage induced by TOP inhibitors is different from that triggered by Pt drugs, that is, majorly intrastrand cross-links from the latter. Indeed, the combination of TOP inhibitors with Pt drugs has been investigated and proved to significantly improve the therapeutic outcomes in several cell lines. To further improve the synergistic effect of TOP inhibitors and Pt drugs, using nanomaterials as a delivery platform to achieve effective tumor targeting and intracellular release of the combined drugs is a promising strategy, and has drawn lots of attention. Yang and coworkers reported the development of an amphiphile by using hydroxycamptothecine (HCPT), a topoisomerase I inhibitor, as the negatively charged moiety; in the presence of cisplatin, the amphiphile could self-assemble into nanofibers or nanoparticles. The formed nanoparticles as the “Trojan Horse” could rapidly accumulate in cancer cells through endocytosis, and then release HCPT and cisplatin. These nanoparticles not only presented great synergistic effects from HCPT and cisplatin, with a combination index (CI) as low as 0.16, but also successfully overcame the drug resistance developed by cancer cells, with up to 75.4-fold increased cytotoxicity than cisplatin in the cisplatin-resistant cells. Besides, such “Trojan Horse” presents an exciting synergistic tumor inhibition effect in an in vivo tumor model, confirming that using nanomaterials to co-deliver Pt drugs with TOP inhibitors is a promising strategy. Nguyen et al. used a single polymer-caged nanobin (PCN) as a drug carrier to co-deliver doxorubicin and cisplatin into cancer cells. After entering cancer cells by endocytosis, the PCN will release doxorubicin and cisplatin in the acidic environment, thus kill the cancer cells. As expected, this nanoparticle presented a high synergistic effect in an in vitro model, with the CI value of 0.34, whereas the CI value of the combination of free doxorubicin and cisplatin was as high as 2.08, suggesting the potential of such nanomaterials to enhance the synergistic effect of conventional combinatorial therapy. Another example is reported by Wang et al. The authors loaded doxorubicin and cisplatin into poly(acrylic acid)-based nanogels, which could effectively accumulate in the cancer cells and release the loaded drugs by a pH/GSH-dual-stimulated fashion (Figure 2A). The CI value of this nanosystem was calculated to be 0.84, indicating the synergistic effect of the loaded drugs. In a xenograft mouse model, the synthetic nanogels exhibited higher tumor accumulation efficiency than the combination of free drugs, thus resulting in more than threefold increased antitumor efficiency (Figure 2B and C), highlighting the advantages of nanomaterials.

For nanomaterials that are difficult to load conventional Pt(II) drugs, Pt(IV) prodrug is an alternative option, as it can be easily functionalized to enhance their compatibility with the nanomaterials. A pioneer study is reported by Du et al. In this work, doxorubicin was packaged in amphiphilic diblock copolymer-based nanoparticles, and a cisplatin-based Pt(IV) prodrug containing two axial alkyne ligands was conjugated with the nanoparticles by click reaction. In vitro studies indicated that the developed co-delivery micelles could be effectively taken by cancer cells, and then they release the loaded drugs to synergistically kill the cancer cells. Consequently, the co-delivery micelles exhibited up to fourfold increased cytotoxicity than the free drugs. Another strategy to co-deliver a Pt(IV) prodrug with a TOP inhibitor is designed by Ang and coworkers. The authors used doxorubicin (DOX) and benzoic acid as the axial ligands to obtain a cisplatin-based Pt(IV) prodrug. Then the DOX-conjugated Pt(IV) prodrug was sealed in multiwalled carbon nanotubes (MWCNT), which were functionalized with a tumor-targeting peptide.
Nanomaterial-driven cotreatment of multichemotherapeutic drugs containing platinum drugs. (A) The design and synthesis of cisplatin/doxorubicin co-delivery nanogels (CDDP/DOX-NGs). (B) The relative tumor volumes and (C) body weight changes of BALB/c nude mice bearing MCF-7/ADR tumors after different treatments (copyright 2017, American Chemical Society). (D) The synthesis and mechanism of nanoscale coordination polymers (NCP-1) containing oxaliplatin-based Pt(IV) prodrug and gemcitabine monophosphate (GMP). (E) The tumor volume and (F) bodyweight changes of subcutaneous BxPc-3 xenografts after different treatments (copyright 2015, Elsevier). (G) The design, synthesis, and mechanism of lipid nanoparticles containing active form of oxaliplatin and folinic acid (FnA) for combinatorial treatment. (H) The tumor volume and (I) survival rate of orthotopic colorectal cancer mice after different treatments (copyright 2020, American Chemical Society).
(c-RGDfK) to enhance the tumor-targeting capacity. After entering cancer cells, the intracellular reduction environment could reduce the Pt(IV) prodrug to cisplatin and DOX, which were intrinsically hydrophilic and therefore would be extruded from the MWCNT vehicle to induce DNA damage and kill the cancer cells. This drug-loaded nanodelivery platform showed more than 11-fold increased cytotoxicity than the free drug and was found to effectively overcome the developed drug resistance in vitro. 

2.2 Co-delivery of Pt drugs with antimicrotubule agents

Microtubules are components of cytoskeleton that are involved in various important cell processes, including maintaining the structure of cells and providing a platform for intracellular transportation, signaling activation, and mitosis. The importance of microtubules in the growth of cancer cells makes them a valuable target for cancer treatment, and several antimicrotubule agents have been developed and approved for clinical treatment. As antimicrotubule agents and Pt drugs present great complementary effects, antimicrotubule agents are frequently combined with cisplatin for the treatment of ovarian and cervical cancers in the clinic. Lots of efforts have been devoted to coloading antimicrotubule drugs with Pt drugs in nanomaterials to realize improved therapeutic outcomes. A validation study was carried out by Farokhzad et al. The authors developed self-assembled polymeric nanoparticles to co-deliver docetaxel and a cisplatin-based Pt(IV) complex, then the nanoparticles were functionalized with a prostate-targeting aptamer for prostate cancer treatment. After entering cancer cells, this co-delivery platform could release both drugs in a controllable manner within 72 hours, resulting in more than 50-fold enhanced cytotoxicity than the free drug in the targeted cells. Interestingly, they found that the drugs loaded in the nanoparticles could synergistically kill the cancer cells, whereas no synergistic effects from free cisplatin and docetaxel were observed, suggesting the nanomaterial-based co-delivery platform might be an advantage. Feng and colleagues loaded docetaxel into D-alpha-tocopheryl-co-poly(ethylene glycol) 1000 succinate (TPGS)-cisplatin prodrug nanoparticles, with herceptin as a cancer-targeting moiety. Improved anticancer efficiency and decreased dosage were observed compared with the free drugs. Notably, the ratio of loaded drugs had a critical impact on the activities of the nanodelivery vehicles; the best ratio of docetaxel to cisplatin was 2.6, at which the anticancer efficiency and synergistic effect of both drugs were maximized, emphasizing the advantage of nanoparticles to flexibly adjust the ratio of packaged drugs. 

Jing and Liu reported a nanomicelle platform to co-deliver paclitaxel (PTX) and a cisplatin-based Pt(IV) prodrug to improve anticancer efficiency and tolerance. The authors conjugated PTX and the Pt(IV) prodrug on two different polymers, then the two modified polymers were assembled to drug-containing micelles. Both in vitro and in vivo experiments evidenced that the PTX/cisplatin carriers had a great synergistic effect with a CI value lower than 0.5. Importantly, the authors analyzed several clinical chemical parameters in an in vivo model. The values of aspartate aminotransferase (AST), creatine kinase (CK), and lactate dehydrogenase in mice treated with free drug combination were more than twofold higher than those in the mice treated with the co-delivery micelle, indicating that such nanodelivery system could effectively reduce hepatotoxicity and cardiotoxicity from the cisplatin/PTX combinatorial treatment, and a higher package dosage for cancer treatment could be achieved by using the system. Kim and coworkers encapsulated cisplatin and docetaxel in liquid crystalline nanoparticles with folic acid as a targeting group for breast cancer treatment. Compared with the combination of free drugs, the tumor volume decreased more than 30%, and no body-weight loss was observed, indicating that the synthetic nanodelivery system had significantly increased tumor inhibitory effect and decreased side effects in vivo.

2.3 Co-delivery of Pt drugs with antimetabolite drugs

An important factor that contributes to the resistance of Pt-based chemotherapy is the elevated ability of DNA repair. Cancer cells can bypass the Pt-DNA adducts to replicate DNA; they may also have increased ability of DNA repair and DNA damage tolerance, resulting in the compromised cell death signaling pathways. Antimetabolite drugs mimic the building blocks to be incorporated into DNA and consequently impair the ability of DNA replication. Therefore, antimetabolites may resensitize resistant cancer cells to Pt drugs by suppressing DNA replication and DNA repair. Indeed, clinical benefit has been observed for the combination of Pt drugs with antimetabolite drugs in several types of cancer. To further optimize the therapeutic outcomes, using nanoparticles as a co-delivery platform to minimize the pharmacokinetic difference of drugs is a promising strategy. Lin et al loaded an oxaliplatin-based Pt(IV) complex and gemcitabine monophosphate (GMP) into a self-assembled nanopolymer (NCP-1) for pancreatic cancer treatment. After cellular entrance, the Pt(IV) complex was reduced to oxaliplatin and induced DNA damage; at the same time, GMP interrupted DNA replication, amplifying the oxaliplatin-induced DNA...
damage (Figure 2D). NCP-1 exhibited more than 1000-fold prolonged circulation time and a sixfold increased tumor-accumulation level than free oxaliplatin in vivo. Consequently, NCP-1 presented an enhanced tumor inhibitory effect compared with the combination of free drugs (Figure 2E and F), highlighting the benefit of nanoparticle-mediated co-delivery of Pt drug with antitumor cell death (ICD), was loaded in Nano-Folox. Intriguingly, the system could effectively trigger ICD in cancer cells to reprogram the immunosuppressive microenvironment of tumors and, thus, convert the immunotherapy-resistant “cold tumor” to the immunotherapy-sensitive “hot tumor.” Consequently, the combination of anti-programmed cell death ligand 1 (PD-L1) monoclonal antibody enhanced the antitumor efficacy of Nano-Folox in the mouse model, suggesting the potential of cotreatment strategy to invoke an immune response.

Taken together, these studies emphasize the feasibility of using nanodelivery platforms to enhance the complementary of Pt drugs with other chemotherapeutic drugs for improved combinatorial cancer therapy.

3.1 Pt chemotherapy combined with organic PS-based PDT

The simplest way to administrate Pt-based chemophotodynamic combinatorial therapy is to simply conjugate Pt drugs (or prodrugs) with PS to form drug-PS self-delivery systems. For example, Liu’s group reported that a PS of meso-tetra(p-hydroxyphenyl) porphine (THPP) was covalently conjugated with a cisplatin prodrug and PEG via a simple one-pot reaction to form a covalent-organic polymer (COP)-based nanomedicine. The percentages of loaded THPP and cisplatin in COPs were 27.8% and 11.7% (40.6% in total), respectively. Thus, the nanomedicine contains a high amount of functional components including cisplatin and THPP in comparison to conventional drug delivery systems, with only about 10-20% loading capacities. In the presence of reducing agents such as glutathione (GSH) at a high level in the tumor, the nanocarriers could be decomposed into active Pt(II) and PS with minimized long-term toxicity. The COP-based combinatorial therapy effectively repressed tumor growth with a tumor growth inhibition rate of near 80% under a low power density of 5 mW/cm², whereas both cisplatin and COPs nanosystem without irradiation exhibited tumor growth inhibition rates of less than 25%, remarkably lower than that of the combinatorial therapy. The PDT was administrated with single treatment under irradiation at 660 nm with a low power density. Thus, the inhibitory effect may be improved by multiple rounds of treatment or irradiation at a higher power density.

Additionally, some nanohybrids based on Pt drugs/prodrugs and PSs were also developed by self-assembly. The well-defined cavity of a discrete organoplatinum(II) metallacage containing a Pt-based anticancer drug was employed to encapsulate PS of octaethylporphine (OEP), serving as dual delivery of chemotherapeutic drug and PS for combinatorial therapy. The formation of host-guest complex facilitated the co-delivery of chemotherapeutic agent and PS with negligible aggregation of PS, which would greatly prompt PDT effect. High tumor accumulation and reduced side effects were achieved due to the enhanced permeability and retention effect and active targeting ability. The nanoplatform showed synergistic antitumor efficacy against a drug-resistant tumor model with 89.2% tumor inhibition under irradiation, compared with 14.1% and 25.5% for cisplatin and the nanoplatform without irradiation, respectively. Meanwhile, organic-based materials are also widely used for drug delivery owing to their excellent biocompatibility. Liposome-based nanoparticles with a bilayer of lipid similar to cell membranes have already been harnessed for drug delivery, such as the clinically approved Doxil for the delivery of doxorubicin. A liposome nanoassembly based on phospholipid was
designed by Yu and Li’s groups for the co-delivery of Pt(IV) prodrug and PS. An oxaliplatin-based prodrug hexadecyl-oxaliplatintrimethyleneamine was synthesized and then assembled with diisopropylethylenediamine-modified Ce6, namely AC, together with phospholipid to form polymeric nanoparticles (Figure 3A). AC is hydrophobic at neutral pH and tends to aggregate; it is protonated under acidic condition and got positively charged to deaggregate. Thus, the acid-activatable capability could enhance the fluorescence with 3.6-fold higher ROS generation at pH 6.2 compared with that at pH 7.4, which is owing to the deaggregation of AC PS (Figure 3B and C). The nanoassembly was capable of acid-triggered precise imaging and PDT with excellent inhibition of tumor growth.

Nanoparticles with large surface areas, such as mesoporous silica nanoparticles, have been broadly employed for drug delivery. Layered double hydroxide (LDH) nanoparticles with layered structure composed of magnesium and aluminum also possess a large surface area for potential drug loading. The positive layers of LDH nanoparticles can form strong electrostatic interactions with anionic therapeutic agents for theranostic applications. We loaded the PS Ce6 and the Pt(IV) prodrug DSCP in LDH for combined PDT and chemotherapy. The nanohybrid displayed a strong anticancer effect in both cisplatin-sensitive and -resistant cells. Compared with cisplatin, the nanostructures showed about 130- to 190-fold elevated cytotoxicity under irradiation in cisplatin-resistant cells, revealing the excellent anticancer efficacy of the nanocarriers. In addition, fluorogens with aggregation-induced emission (AIE) characteristics can act as PS, which were conjugated with Pt(IV) prodrug and peptide for photodynamic chemotherapy. The AIE PSs conjugated with Pt(IV) prodrug had high sensitivity to reducing agents such as ascorbic acid and GSH, and the system was almost nonemissive in aqueous solutions. The conjugates could be lighted up in the reducing condition of tumor to obtain the PDT effect; they also had the ability to monitor drug activation in real-time in cancer cells. The conjugates showed anticancer effect in both cisplatin-sensitive and -resistant cells; in comparison to the chemotherapy alone, the chemo-photodynamic combinatorial therapy exhibited 8.8-fold increased cytotoxicity in cisplatin-resistant MDA-MB-231 cells.

Upconversion nanoparticles (UCNPs), which are excited by near-infrared (NIR) light and emit visible or ultraviolet light, are ubiquitous theranostics due to their specific optical properties. They are used in biosensing, imaging, drug delivery, and PDT. NIR-excitation of UCNPs enables deep-tissue penetration for PDT and low-autofluorescence for bioimaging. Our group has reported the use of core-shell UCNPs as nanocarriers for PDT and chemotherapy. These UCNPs have an excitation wavelength of 808 nm rather than the traditional 980 nm. As the former wavelength would induce less overheating, these UCNPs would be more suitable for PDT involving prolonged irradiation. To this end, we covalently conjugated poly(acrylic acid)-modified UCNPs to Pt(IV) prodrugs and Rose bengal (RB) to create a possible combinatorial therapy. Upconversion emission at approximately 550 nm excites RB for PDT, and emission at 660 nm can be utilized for bioimaging. This nanoplatform displayed excellent cell-killing efficiency in both cisplatin-sensitive and -resistant cells, equivalent to a 14.5- and 12.3-fold higher anticancer effect, respectively, than that of free cisplatin. Thus, this nanoplatform is a potential nanotheranostic approach to combat drug resistance for imaging-guided cancer therapy.

Photoactivatable Pt(IV) prodrugs can be reduced to highly toxic Pt(II) species under irradiation and can also be utilized for drug delivery by UCNPs. Yan’s group reported that a Pt(IV) complex of c,t,c-[Pt(N3)2(OH)2(NH3)2] with photoactivatable property was conjugated with PS to form an amphiphilic oligomer Ce6-PEG-Pt(IV), which was subsequently loaded on UCNPs for combined therapy (Figure 3D). The UCL emissions of core-shell UCNPs at around 365 and 660 nm could be used for Pt(IV) photoactivation and Ce6 excitation, respectively. Remarkably, besides the production of cytotoxic Pt(II) species under NIR irradiation, the Pt(IV) complex was able to act as an effective O2-self-generating moiety for PDT application. The UCNPs loaded with PEG-Pt(IV) (UPP) prompted the O2 concentration under irradiation with a 980 nm laser, whereas the Ce6-loaded nanosystem (UPC) reduced the O2 concentration because the PDT administration would consume O2 (Figure 3E). The nanosystem loaded with Ce6-PEG-Pt(IV) (UCPP) displayed the greatest ability to generate ROS compared with Ce6- or Pt(IV)-loaded systems, showing that the nanoplatform can efficiently generate ROS independent of normoxic or hypoxic environment (Figure 3F). By monitoring the two typical indicators of hypoxia level, hypoxia-inducible factor-1α (HIF-1α) and CD31, the UPP nanosystem was able to reverse the hypoxia with the lowest levels of HIF-1α and CD31 due to the self-generation of O2 from the Pt(IV) prodrug under irradiation (Figure 3G). Four types of xenograft tumors treated with UCPP together with laser irradiation were evaluated, and the nanosystem showed superior antitumor activities and minimal side effects. In HeLa, HCT116, and MDA-MB-231 tumor-bearing mice treated with UCPP under NIR irradiation, the tumors all disappeared, while the tumors of other groups grew fast with at least more than 350% increased tumor volumes. In B16 tumor-bearing mice, two of five mice were completely healed by the chemo-PDT. These in vivo antitumor outcomes indicate the excellent synergistic performance of combinatorial
FIGURE 3  (A) Chemical structures of the components as well as the formation of nanoconstruct for organelle-specific imaging and PDT/chemotherapy. (B) ROS generation of AC-loaded prodrug NPs at different pH upon irradiation with a 655 nm laser. (C) Schematic illustration of protonation-induced deaggregation and activation of AC PS in the acidic condition\textsuperscript{45} (copyright 2016, Wiley). (D) Schematic illustration of the formation of UCPP nanoparticles. (E) Oxygen concentration of UPP, UCPP, and UPC under 980 nm irradiation. (F) The generation of ROS of UPP, UCPP, and UPC under 980 nm irradiation. (G) Immunofluorescence staining of HIF-1α (green) and CD31 (red) on HeLa tumor slices with irradiation\textsuperscript{51} (copyright 2018, Nature Publishing Group). (H) Scheme of the photoactivable polyprodrug formation and its antitumor mechanism. (I) Tumor growth curves in A549 and A549R xenografted mouse model after intravenous injection\textsuperscript{54} (copyright 2018, Elsevier)
photo-chemotherapy with a promising potential for preclinical applications.

In addition to the traditional organic PSs, Ru(II)-based complexes are able to generate ROS under irradiation, and they have the advantages of water solubility, cell permeability, and resistance to photobleaching. Therefore, Ru(II)-based complexes are also widely used as PS for PDT.\textsuperscript{52} The ligands in Ru(II)-based complexes can be designed to gain the customized excited states with the ability to respond to visible light for PDT.\textsuperscript{52a} A 3D octahedral metallacage was designed through the self-assembly of Ru(II)-based PS and complementary Pt(II)-based building blocks.\textsuperscript{53} The 3D metallacage was encapsulated into 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)-mPEG2000 to form nanoparticles with two-photon excited PDT effects by NIR. The Ru-Pt bimetallic metallacage with a large two-photon absorption cross-section was capable of generating ROS efficiently under irradiation. The metallacage displayed effective chemo-photodynamic efficiency in vivo against cancer growth. The nanosystem-treated mice only had 65.2% of the original tumor volume upon irradiation.

Furthermore, it is claimed that cisplatin-based Pt(IV) prodrugs can act as both chemotherapeutic agents and PSs. The in situ polymerization of Pt(IV)-based prodrug monomer (PPM) together with 2-methacryloyloxyethyl phosphorylcholine (MPC) was harnessed to obtain a copolymer that could form nanosized hydrogel-like hyper-branched polyprodrug (polyPPM) for chemo-PDT (Figure 3I).\textsuperscript{54} The polyPPM nanoconstruct was capable of O\textsubscript{2}-independent ROS self-generation without the administration of another PS. This polyPPM nanosystem generated cytotoxic Pt(II) species and ROS under irradiation, serving chemotherapy and PDT simultaneously. In comparison to cisplatin, the polyPPM under irradiation exhibited 4.9- and 10.4-fold increased cytotoxicity in cisplatin-sensitive A549 and cisplatin-resistant A549R cells, with IC\textsubscript{50} values of 2.6 and 2.9 \textmu M, respectively. A549 and A549R tumors treated with polyPPM upon irradiation almost disappeared, and some of the mice were fully cured after the treatment. Therefore, this nanosystem exhibited an efficient antitumor effect in both cisplatin-sensitive and -resistant tumor models (Figure 3l).

3.2 | Pt chemotherapy combined with inorganic PS-based PDT

Besides the organic PSs mentioned above, some inorganic components are also employed for PDT. ZnFe\textsubscript{2}O\textsubscript{4} with a narrowband gap of \textasciitilde 1.9 eV is widely used in catalysis. In a report by Lin’s group, ZnFe\textsubscript{2}O\textsubscript{4} nanoparticles were used as an effective PS for PDT, and they were bonded to Pt(IV) prodrugs-modified UCNPs.\textsuperscript{55} The ZnFe\textsubscript{2}O\textsubscript{4} nanoparticles were also utilized to exert chemodynamic therapy through Fenton reaction to release toxic •OH, and the nanoconstruct served as a multimodal bioimaging tool including UCL, CT, MR, and photoacoustic (PA) imaging in vivo. This smart all-in-one imaging-guided theranostic nanoplatform with an effective antitumor effect provided a promising approach to treat cancer. The nanoplatform with NIR irradiation showed 1.4-fold enhanced antitumor effect than that with UV irradiation. The relative tumor volume in mice treated with the nanoplatform upon NIR irradiation increased only about 1.4-fold of the original size, significantly lower than those in mice treated with single chemotherapy or PDT only. These in vivo antitumor performances demonstrate the outstanding synergetic chemo-photodynamic anticancer effect from the nanoplatform.

In addition, two-dimensional MnO\textsubscript{2} nanosheets serve as a nanocarrier for Au nanoclusters (Au\textsubscript{25}), a PDT agent, and Pt(IV) prodrug, forming a nanoplatform (MnO\textsubscript{2}-Pt@Au\textsubscript{25}) for chemo-dynamic therapy.\textsuperscript{56} The MnO\textsubscript{2} nanosheets were reduced to Mn\textsuperscript{2+} in the presence of a high level of GSH in cancer cells. Concomitantly, the Pt(IV) prodrugs were transformed into cytotoxic Pt(II) species by GSH, acting as chemotherapy to further decrease the GSH level. Consequently, the depletion of GSH by reacting with MnO\textsubscript{2} and Pt(IV) could decrease the consumption of 1O\textsubscript{2} due to the reducing ability to cellular ROS; thus it would significantly improve the PDT efficiency. The MnO\textsubscript{2} nanosheets under H\textsubscript{2}O\textsubscript{2} and acidic tumor microenvironment were reduced to Mn\textsuperscript{2+} to generate O\textsubscript{2}, which can further improve the PDT effect by relief of the hypoxia condition. The tumor treated with MnO\textsubscript{2}-Pt@Au\textsubscript{25} nanosheets and irradiated with a 650 nm laser had the lowest volume, even smaller than the original tumor. On the other hand, the MnO\textsubscript{2}-Pt and MnO\textsubscript{2}-Au\textsubscript{25} groups with irradiation displayed about 8.5- and 3.1-fold increased tumor volumes, respectively. Thus, this nanosystem displayed an excellent chemo-dynamic therapeutic effect and can be utilized for GSH- and H\textsubscript{2}O\textsubscript{2}/H\textsuperscript{+}-responsive and MRI imaging-guided theranostics of cancer.

4 | COMBINATION OF PLATINUM CHEMOTHERAPY WITH PTT

In PTT, photon energy is converted to heat energy to locally destroy cancer cells, and PTT has gained increasing attention for combating solid tumors.\textsuperscript{57} The photo-induced local hyperthermia effects increase tumor vascular permeability, leading to enhanced accumulation of nanoparticles at the tumor site. Moreover, the hyperthermia also increases permeability of the cell membrane, which promotes the
uptake of chemotherapeutics into cancer cells. It has been observed that cisplatin has enhanced cytotoxicity at elevated temperature. For instance, at the temperature of 43.5°C, the thermal enhancement ratio of cytotoxicity for cisplatin is 1.5. Therefore, combining cisplatin with PTT is able to decrease the dose of cisplatin to achieve comparable anticancer activity from single treatment, which is expected to have minimized systemic side effects. In addition, the cytotoxic pathway of heating-induced cell death is different from that of cisplatin. PTT may also effectively kill cisplatin-resistant cells. Thus, the combination of platinum drugs with PTT holds great promise to enhance cytotoxicity, reduce systemic side effects, and overcome resistance.

4.1 Delivery of Pt drugs by nanomaterials with PTT effects

One way to achieve the combinatorial therapy is to load platinum drugs to nanoparticles with photothermal properties such as gold nanomaterials with various structures, palladium nanosheets, CuS, CuFeS₂, and graphene oxide. Gold nanomaterials are biocompatible and size controllable, and they show strong absorption in the NIR region due to the surface plasmon resonance (SPR) effect. The photothermal effect of gold nanomaterials upon NIR irradiation has been widely used for photothermal therapy, and the combination of gold nanomaterials with platinum drugs has been investigated recently. The first example of such combination is reported by Jiang et al.⁵⁹ They integrated gold nanorods (GNRs) and cisplatin into nanoparticles formed by chitosan with a size of 120 nm. The nanohybrid showed extraordinary antitumor effects in HT22 tumor-bearing mice upon NIR irradiation. The tumor volume of the cisplatin-treated group reduced only 50% compared with the saline group on day 18. The mice with single PTT treatment showed 85% reduction in the tumor volume. Notably, the combination of cisplatin with PTT almost completely stopped the tumor growth. No visible tumor was observed in the treated mice. These encouraging results suggest that the combination of cisplatin with PTT has superior antitumor outcomes compared with the single therapy.

Subsequently, oligonucleotide-modified GNRs,⁶⁰ poly-peptide-wrapped GNRs,⁶¹ triangular and multicore Au@polymer nanoparticles,⁶² tripeptide-tethered hollow gold nanoparticles,⁶³ and gold nanoshells⁶⁴ are also reported to deliver platinum drugs to achieve combinatorial therapy. A multifunctional chemothermal therapy is reported by Zhang and coauthors.⁶⁵ They prepared RGD-IPT-PDA@GNRs by functionalization of GNRs with polydopamine (PDA) and PEG to increase biocompatibility, with arginine-glycine-aspartic acid (RGD) peptides to enhance tumor targeting properties, and with iodine-125 for imaging (Figure 4A). The active form of cisplatin, [[(Pt(H₂O)₂(NH₃)₂)₂]²⁺], was loaded to the nanoparticles. RGD-IPT-PDA@GNRs could specifically target α₅β₃ integrin-positive H1299 cancer cells and achieve imaging-guided therapy. The H1299 tumors in mice treated with the combinatorial therapy were eliminated on day 3 posttreatment and no tumor relapse was observed (Figure 4B), whereas the tumor recurrence was found in 40% of mice treated with single PTT. This result suggests that PTT alone may damage the cancer cells, but in addition to PTT, platinum drug suppresses the proliferation and self-repair of the damaged cancer cells to inhibit tumor recurrence. Additionally, the systemic toxic effects of RGD-IPT-PDA@GNRs were investigated by histological analyses of major organs in mice 21 days posttreatment. No noticeable organ damages were observed, indicating the safety of the nanohybrid.

Copper chalcogen materials have been developed as novel PTT agents due to their low toxicity, simple preparation, and high photothermal conversion efficiency in the NIR region. Reported by Yang’s group, the Pt(IV) prodrug DSCP was conjugated to the surface of CuS NPs.⁶⁶ The NPs were further modified with folate-conjugated PEG to endow targeting and biocompatibility. Under irradiation at 980 nm, the photothermal conversion efficiency (η) of CuS NPs was calculated to be 32.1%, which is much higher than that of Au nanorods (η = 22%). In U14 tumor-bearing mice, CuS-Pt(IV) NPs completely stopped the tumor growth upon irradiation. Lin et al prepared CuFeS₂ for PTT application.⁶⁷ Chitosan (CS), a linear cationic polysaccharide, was introduced to the surface of CuFeS₂ to improve the water solubility, biocompatibility, and stability. In this system, DSCP was conjugated through an amide reaction. The nanocomposite showed a strong absorption at 808 nm, with a photothermal conversion efficiency of 30.5%. Owing to its significant NIR absorption capability, the particles could achieve in vivo PA/PT dual-modal imaging. CuFeS₂-CS-Pt with irradiation achieved remarkable anticancer effects in mice bearing A549 tumor, and the tumor was eliminated completely in two of four mice. Chang et al coated CuFeS₂ with HA and loaded DSCP to yield CuFeS₂@HA-Pt(IV) for combinatorial therapy.⁶⁸ The hybrid displayed a superior high photothermal conversion efficacy of 74.2% and significantly inhibited B16F1 cancer cell proliferation.

Besides gold and copper chalcogen nanomaterials, graphene oxide,⁶⁹ carbon nanotube,⁷⁰ MoS₂, nanoflower,⁷¹ ion oxide,⁷² melanin nanoparticles,⁷³ and black phosphorus nanosheets⁷⁴ have also been used for the delivery of platinum drugs to achieve the combination of platinum chemotherapy with PTT. In addition, nanocomposites...
FIGURE 4  (A) Schematic illustration of the preparation procedure for RGD-^{125}Pt-PDA@GNRs nanodrugs; (B) tumor growth curves of mice bearing H1299 tumors after different treatments (reproduced with permission; \textcopyright 2016, American Chemical Society). (C) Scheme of NIR-stimuli CDDP release from amphiphilic polymer (PEG-PUTe-PEG)-based nanoparticles and the proposed blood circulation, drugs accumulation, and release at the tumor sites; (D) cisplatin release profile of NPs-Pt-ICG upon NIR irradiation; (E) tumor growth curves of mice bear-
made up of two different PTT materials have been applied for the delivery of platinum drugs. Chen et al. reported the growth of Au on the surface of Pd nanosheets to yield Pd@Au nanoparticles. Both Au and Pd nanosheets could generate heat under NIR irradiation. The Pd@Au nanoparticles were further modified with thiol-polyethylene glycol-amine (SH-PEG5000-NH₂) to increase biocompatibility. Then, DSCP was loaded by conjugation with the amine group on the PEG. Upon irradiation with an 808 nm laser, the Pd@Au-PEG-Pt nanocomposite efficiently generated heat, and the increased temperature also facilitated the chemical reduction of the preloaded Pt(IV) prodrug by ascorbic acid. The nanocomposite had high tumor accumulation, and the combined chemotherapy and PTT completely suppressed tumor growth in mice bearing S180 tumors.

### 4.2 Co-delivery of Pt drugs and organic PTT agents using nanoparticles

Another way to realize the combinatorial chemothermal therapy is to coload Pt drugs and PTT agents, such as cyanine dyes and dopamine, to polymer-based nanoparticles or by self-assembly. These organic nanoparticles have advantages in biocompatibility and biodegradability. Indocyanine green (ICG) is an FDA-approved clinical diagnostic and imaging agent, which can also be used as an excellent PTT and PDT agent due to its strong absorption in the NIR region. Co-delivery of ICG with Pt drugs has been achieved by loading ICG into the core of cisplatin prodrug-constructed liposomes or by coencapsulation of cisplatin and ICG to liposomes. A typical example is reported by Xu’s group. They prepared a tellurium-containing polymer-based drug delivery system (NPs-Pt-ICG), in which cisplatin was loaded via the coordination of Pt with Te, and ICG was encapsulated into the core of the formed micelles (Figure 4C). In the dark, NPs-Pt-ICG only lost less than 20% cargos even after 5 days, indicating the great stability of the nanoparticles. The system displayed a prolonged circulation time and enhanced accumulation in the tumor site, leading to less systemic side effects from the results of bodyweight, serum biochemical tests, and H&E staining of major organs of drug-treated mice. Upon irradiation, the singlet oxygen generated from ICG oxidized the tellurium on backbone of the polymer, resulting in rapid release of cisplatin from the nanoparticles (Figure 4D). The combined photothermal effects, generation of singlet oxygen, and platinum chemotherapy resulted in powerful anticancer effects in an MDA-MB-231 tumor model; the tumors in two mice completely disappeared (Figure 4E). This work highlights the advantage of utilizing NIR-triggered heat or ROS to achieve local release of the encapsulated platinum to reduce the side effects, and combination of multiple therapies is able to synergistically improve the antitumor outcomes.

Recently, Dai et al. also developed a drug delivery system by coloading 1,2-diaminocyclohexane-platinum(II) (DACHPt), the active form of oxaliplatin, and ICG to anionic bovine serum albumin nanoclusters to yield BPtI. The surface of BPTI was further coated with red blood cell membranes modified with cRGD (R-RBC) to minimize drug leaking and intake by macrophage. The cRGD group enhances the accumulation of NPs in various malignant tumors that overexpress αvβ3 integrin. As expected, the as-prepared R-RBC@BPtI displayed high immune escape and tumor-targeting capabilities with prolonged circulation time and enhanced tumor accumulation. Upon irradiation, the generated singlet oxygen and heat by ICG disrupted the RBC membrane, leading to the release of Pt and ICG to achieve chemotherapy and PTT/PDT, respectively. This combination resulted in effective tumor ablation and suppression of metastasis, with 93% reduction of lung metastases of melanoma. This work suggests that chemo-phototherapy holds the potential for inhibiting lung metastasis of melanoma. Except for ICG, cypate, PDA, and polyaniline were also used as PTT agents in combination with platinum drugs to achieve nanomaterial-mediated combinatorial therapy.

The ability of combined chemotherapy and PTT to combat cisplatin resistance was also studied recently. Chen et al. coloaded a cisplatin prodrug (c,t,c-[Pt(NH₃)₂(CO₂CH₂CH₂CH₂CH₂CH₃)₂Cl₂]) and a PTT agent, cypate, into micelles based on mono-methoxy poly(ethylene glycol) and decylamine-grafted poly(L-aspartic acid) (mPEG-bPAsp, Figure 4F). The P/C-micelles showed enhanced cellular accumulation in cisplatin-sensitive A549 and cisplatin-resistant A549R cells via endocytic pathways. Upon irradiation, singlet oxygen was generated and caused lysosome escape of the P/C-micelles. Cisplatin and cypate were released in a sustained fashion from the P/C-micelles. Notably, the photo-induced hyperthermia inhibited the expression of MDAMB-231 tumors after different treatments (reproduced with permission; copyright 2017, Elsevier Ltd.) (F) Schematic illustration of the micelles encapsulating Pt(IV) prodrug and cypate (P/C-Micelles); (G) western blotting analysis of the MRP1 levels in A549 and A549R cells after different treatments; (H) tumor growth profiles of the mice bearing A549R and A549 tumors after different treatments (reproduced with permission; copyright 2015, American Chemical Society).
MRP1, a protein related to cisplatin resistance (Figure 4G). The P/C-micelles exhibited higher cytotoxicity in both cisplatin-sensitive A549 and cisplatin-resistant A549R cells; the resistance factor was 5.4 for cisplatin, while the value was 1.17 for the P/C-micelles. Remarkably, in a tumor xenograft model, the P/C-micelles could ablate both A549 and A549R tumors and no regrowth of tumor was observed after 8 days postirradiation (Figure 4H). This is the first example of eliminating cisplatin-resistant tumor by intravenous administrable nanodrugs. Recently, Hu et al prepared enzyme-degradable amphiphiles containing a cisplatin prodrug $c,c,t[\text{Pt(NH}_3)_2\text{Cl}_2(\text{OH})_2]$. ICN was subsequently encapsulated into the amphiphilic self-assembled micelles; denoted as ICG/Poly(Pt). After the entrance of ICG/Poly(Pt) in lysosome, cathepsin B degraded the nanostructure to release ICG and the cisplatin prodrug for PTT and chemotherapy, respectively. As indicated in their in vivo tumor ablation assay using a cisplatin-resistant A549R model, mice treated with ICG/Poly(Pt) upon NIR irradiation completely suppressed tumor growth, and some tumors were even totally eradicated. More importantly, the mice treated with photoactivated ICG/Poly(Pt) had a median survival time of 60 days, which was significantly longer than other groups, for example, cisplatin with irradiation (27 days), ICG with irradiation (33 days), and Poly(Pt) (42 days). These results indicate that the combination of cisplatin with PTT is able to combat cisplatin-resistant tumors and obtain prolonged survival time.

The PTT agents mentioned above were activated by light in the NIR-I window (750-1000 nm). Tumor penetration depth is deeper in the NIR-II window (1000-1400 nm), which is superior to the NIR-I window. Thus, the development of PTT agents that can be activated in the NIR-II window is attractive, and combination of PTT agents in the NIR-II window with cisplatin has also been reported recently by Shen et al. The authors constructed a supramolecular hydrogel by using a conjugated polymer (poly(N-phenylglycine)), PEG, and $\alpha$-cyclodextrin ($\alpha$-CD). Cisplatin was loaded into the hydrogel, and upon irradiation at 1064 nm, heat was generated together with the on-demand release of cisplatin. The cisplatin-loaded hydrogel completely suppressed the tumor growth in MDA-MB-231 tumor-bearing mice under laser irradiation with a low power density (1064 nm, 0.5 W/cm$^2$).

These reports indicate that nanomaterial-based combination of Pt drugs with PTT can improve the therapeutic effects of Pt drugs, combat cisplatin resistance, and reduce systemic toxicity. The combinatorial therapy can completely stop tumor growth in most reports. However, the survival time of mice is not significantly improved or not reported in many studies. Further developments may focus on the long-term toxicity of the nanohybrid, the mechanism of the superior antitumor efficacy, and translation into the clinic.

5 | COMBINATION OF PLATINUM CHEMOTHERAPY WITH IMMUNOTHERAPY

Typically, cancer cells are heavily transformed cells that may be recognized as potential targets by the immune system. However, various cytokines that enhance the growth of tumor cells and suppress the function of immune cells are produced in the tumor microenvironment (TME). The emergence of cancer immunotherapy, including immune checkpoint inhibitors, adjuvants, and agonists, has led to remarkable successes in reversing such immunosuppression in TME, but obstacles remain. For example, cancer immunotherapy is insufficiently potent as a monotherapy to be curative, due to the low response rate in patients. Recently, Pt-based chemotherapeutic drugs are found to not only kill the cancer cells directly via cytotoxic effects but also to stimulate the immune system via “off-target effects” to produce antigens or induce ICD (Figure 5). Nevertheless, despite the synergies achieved by the combination of free Pt-based drugs and immunotherapeutics, such combined treatments have performed poorly in both animal models and clinical evaluations. Improved drug-delivery systems are therefore needed to enhance drug accumulation within tumors, to improve cancer treatment, and to reduce systemic toxicity. Nanovehicles such as nanoparticles have been used for this purpose due to their high specificity, efficacy, and therapeutic effects. A summary of nanoparticle-based combinatorial therapy is given in Table 1.
| Pt-based complex | Immuno-regimen | Nanocarrier | Treatment | Reference |
|------------------|----------------|-------------|-----------|-----------|
| Oxaliplatin      | PD-L1 trap     | Lipid-protamine-DNA nanoparticle for the immuno-regimen | Orthotopic CT26 murine colon cancer, B16F10 murine melanoma, and 4T1 murine breast cancer | 97 |
| Oxaliplatin + photosensitizer pyropheophorbide-lipid | PD-L1 antibody | Nanoscale coordination polymer (NCP) core-shell nanoparticles for the Pt complex and the PS | CT26 and MC38 murine colon cancer, and HT29 human colorectal cancer | 98 |
| Oxaliplatin prodrug + PEGylated photosensitizer | Anti-CD47 antibody | Acidity and matrix metalloproteinase-2 (MMP-2)-sensitive prodrug vesicle for the Pt complex and the PS | CT26 murine colon cancer, 4T1 murine breast cancer, and B16F10 murine melanoma | 99 |
| Oxaliplatin      | Indoximod prodrug, an IDO inhibitor | Mesoporous silica NPs (MSNPs) encapsulation as a dual carrier | Orthotopic KPC murine pancreatic cancer | 103 |
| Cisplatin prodrug, c,c,t-[diaminedichlorodisuccinchelatoplatinum(IV)] (DSCP) |IDO inhibitor | Layered double hydroxide nanoparticles as a dual carrier | HeLa human cervical cancer | 104 |
| PEGylated oxaliplatin prodrug | NLG-919 prodrug, an IDO inhibitor | Binary cooperative prodrug nanoparticle (BCPN) as a dual carrier | 4T1 murine breast cancer | 105 |
| Cisplatin prodrug-functionalized phospholipid (DSPE-PEG(2000)-Pt(IV)) | Polynosinic-polycytidylic acid (poly(I:C)) | Iron oxide nanoparticles (IONPs) micelles as a dual carrier | PC-3 human prostate adenocarcinoma, MDA-MB-231 human triple negative breast cancer, and PANC-1 human pancreatic cancer | 106 |
| Dichloro(1,2-diaminocyclohexane) platinum (II) (DACHPt) | WKYMVm peptide (Wpep) | Dendrigraft polylsine (DGL)-based platform as a dual carrier | MDA-MB-231 human triple negative breast cancer and 4T1 murine breast cancer | 107 |
| Lipid-coated cisplatin | Unmethylated cytosine-phosphorothioate-guanine containing oligodeoxynucleotides (CpG-ODN, or CpG) | Liposome for the immuno-regimen | B16F10 murine melanoma | 109 |
| Cisplatin        | Interleukin-15 | Hydrogel as a dual carrier | B16F0-RFP murine melanoma | 112 |
| BODIPY-conjugated cisplatin prodrug | Tumor-associated macrophages | PLGA-b-PEG for the Pt complex | HT1080 human fibrosarcoma and A2780cisR human ovarian cancer | 113 |
| Oxaliplatin prodrug conjugated with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) | Alkylated NLG-919 | Phospholipid as a dual carrier | CT26 murine colon cancer | 114 |
5.1 Combination of Pt drugs with immune checkpoint inhibitors

Immune checkpoints are usually manipulated by tumor cells to evade immunosurveillance from the immune system. The emergence of immune checkpoint inhibitors has reversed the condition and achieved ground-breaking success in clinics, especially in the treatment of melanoma. However, the inhibition efficiency of current immune checkpoint inhibitors was only evidenced to restrain limited types of cancer. Moreover, patients receiving immune checkpoint therapy suffer from low response rates and innate or acquired resistance during or after the treatment. To overcome these drawbacks, a combinatorial strategy with chemotherapy is taken into consideration. Such combination also extends the treatment of cancer types to various solid and liquid cancers.

As a cytotoxic chemotherapeutic drug, oxaliplatin is newly recognized as an immunomodulator to enforce its anticancer effect utilizing mechanisms such as induction of ICD. Oxaliplatin-stressed tumor cells can augment the maturation and attraction of dendritic cells (DCs) and ultimately enhance T-cell responses in tumors. These observations indicate that oxaliplatin can be applied not only as a cytotoxic drug to kill cancer cells directly but also help to recruit more anticancer immune cells in the TME. With the delivery of nanoparticles, the drugs can be transported to targeting tissues with less systematic adverse effects.

To address low immune response rate and immunorelated adverse effects (irAEs) of the current checkpoint inhibitors, Huang’s group reported the combination of free oxaliplatin with a PD-L1 trap fusion protein to transmit the TME from immunosuppression to “hot spots” of the immune response in cancers with low immune response rate. They first demonstrated that the incorporation of oxaliplatin could boost PD-L1 blockade immunotherapy in CT-26 tumor model, which had a low response to anti-PD-L1 mAb therapy. The abundant checkpoint proteins and immunosuppressive cytokines were also found in the TME, which limited the function of tumor-infiltrated T cells. Subsequently, oxaliplatin was combined with PD-L1 trap plasmid-loaded lipid-protamine-DNA (LPD) nanoparticles (Figure 6A and B). After treatment, the tumor size showed a more than seven-fold decrease compared to the monotherapies (Figure 6C and D); the mean survival time prolonged from 47 days in the oxaliplatin group to 56 days in the combinatorial therapy (Figure 6E). Using this novel combination, the immunosuppressive TME was revoked and more transient local intratumor cytotoxic T-lymphocytes (CTL) were recruited to enhance cancer treatment with a low tendency of irAEs. Besides the bifunctional nanoplatform mentioned above, some multifunctional nanoplatforms against various cancer types were also engineered to combine chemotherapy and checkpoint blockade immunotherapy with additional PDT. For example, Lin et al established nanoscale coordination polymer (NCP) core-shell nanoparticles (NCP@pyrolipid) to combine oxaliplatin in the core and pyropheophorbide as a PS in the lipid (pyrolipid). A colon tumor model was established by subcutaneous injection of MC38 cells into both the right and left flank of each mouse to form primary and secondary tumors. The NCP@pyrolipid was injected prior to 670 nm irradiation on the primary tumor, followed by anti-PD-L1 therapy. Such combinatorial therapy could not only eradicate/suppress the primary tumor but also nearly eliminate the secondary tumor, although the irradiation only applied to the primary one. The shrink of the primary and secondary tumors was induced by PD-L1 blockade and NCP@pyrolipid-mediated tumor-specific immune response, such as increased proportions of tumor-infiltrating CD4+ and CD8+ T cells as well as CD45+ leukocytes (regulator of T- and B-cell antigen receptor signaling). For example, the densities of CD8+ in secondary tumors showed a 7.7-fold increase after treatment with the NCP@pyrolipid and PD-L1 blockade, compared with the group treated with PBS only. Li and Yu’s groups prepared acidity and matrix metalloproteinase-2 dual-activable vesicles containing an oxaliplatin prodrug and a PEGylated PS, and the nanocomplex was combined with CD47-mediated immunotherapy. After treatment, five-sixths of primary tumors were completely eradicated, and complete regression of abscopal tumors in a bilateral CT26 model was achieved. Such combinatorial therapy also endowed mice with lasting and specific antitumor immune memory effect to prevent tumor recurrence.

Except for the ligands or receptors expressed on the surface of T cells or tumors, a number of alternative immune checkpoint proteins regulate tryptophan metabolism for T-cell activation in the TME, and they have also been studied recently. Indoleamine 2,3-dioxygenase (IDO) is a prominent example in this class of mechanism. IDO works as a vital enzyme in the tryptophan metabolic pathway and induces tryptophan depletion, resulting in the inhibition of antitumor T cells’ immune activity and evasion of cancer cells from immunosurveillance. After the discovery of the first IDO inhibitor, indoximod (1-methyl-D-tryptophan, D-1MT), several IDO inhibitors have entered clinical trials. However, the tumor inhibition from IDO inhibitors as monotherapeutic drugs cannot reach a satisfying outcome. Subsequently, IDO inhibitors were combined with chemotherapeutic drugs. With the delivery of such combination, rapid regression of tumors was achieved in vivo. Some typical examples were reported based on this strategy. Meng and Nel combined oxaliplatin and indoximod in dual-delivery nanovesicles based on...
FIGURE 6  The nanovehicles to combine Pt-based chemotherapy and immunotherapy for cancer treatment. (A) Scheme illustrating the tribody interaction of PD-L1 trap protein. (B) Preparation of PD-L1 trap plasmid-loaded LPD. (C) Schedule of oxaliplatin and PD-L1 trap cotreatment in the orthotopic CT-26-FL3 tumor model. (D) Tumor growth curves of orthotopic CT-26-FL3 tumors with various groups indicated. (E) Mice survival curves of orthotopic CT-26-FL3 tumors in various treated groups. © Copyright 2018, Springer Nature. (F) Scheme of a nanohybrid
mesoporous silica nanoparticles against pancreatic ductal adenocarcinoma (PDAC). The innate and adaptive anti-PDAC immunity was induced in a vaccination approach through oxaliplatin-mediated ICD. After co-delivery of oxaliplatin and indoximod, tumor reduction or eradication was achieved by recruiting CTL, concomitant with the downregulation of Foxp3+ regulatory T cells (Tregs). In the combinatorial treatment, the ratio of CD8+ /Tregs cells increased about eight times compared to that in the saline group. Our group reported a nanohybrid based on LDH nanoparticles loaded with DSCP and a potent IDO inhibitor (IDOi), with an aim to enhance T-cell proliferation and boost chemotherapy treatment against cervical cancer (Figure 6F). The cancer cell-killing effect from the nanohybrid has improved more than 11.7 times compared with the monotherapies. Meanwhile, the reduction of metabolites from the tryptophan pathway was achieved by IDOI in the nanohybrid, leaving more tryptophan for T-cell activation and proliferation. In the in vitro test, human peripheral blood mononuclear cells were applied to mimic the immune microenvironment and cocultured with HeLa cells. After treatment with the nanohybrid, about 42% proliferated T cells were observed, much higher than those in the untreated group (5.6%) and the group treated with a combination of free IDOi and cisplatin (35.2%) (Figure 6G). A more than twofold decrease of tumor size was achieved in vivo with the help of the immune system (Figure 6H). A similar construct was also reported by Li’s group. The authors assembled tumor acidity-sensitive binary cooperative prodrg nanoparticles containing an oxaliplatin prodrug and a prodrug of IDO inhibitor NLG919. The system elicited antitumor immunity in both breast and colorectal cancer models.

5.2 Combination of Pt drugs with other types of immunotherapy

Apart from the examples mentioned above, some other types of immunotherapy including adjuvants, cytokines, and agonists were also explored for the combination with Pt drugs. Mareque-Rivas’s group reported one of the first combinations of Pt with adjuvants. They prepared iron oxide nanoparticles (IONPs) to co-deliver DSCP and immunostimulatory adjuvant polyinosinic-polycytidylic acid (poly(I:C)) (Figure 6I). Despite the cancer-killing capability, the nanoplatform was confirmed to activate DC maturation. Bone marrow-derived dendritic cells were extracted from mice and cultured with the dual-functional nanoparticles. After incubation for 24 hours, the level of secreted immunopotentiator cytokine IL-12 increased more than twofold, compared with the other monotherapies. The maturation of DC was also confirmed after costimulation by the dual-functional nanoplatform (Figure 6J). These matured DCs could subsequently instruct the activation of CD4+ and CD8+ T-cell-mediated immune response to achieve an enhanced cancer treatment. Jiang’s group reported the combination of DACH/Pt and WKYMVm peptide (Wpep) in the core of dendrigrift polysyline, termed as Wpep-DG/Pt. After treatment with Wpep-DG/Pt, cytotoxic Pt drugs induce cell death and apoptotic tumor cells, which could release antigens and immune signals to antigen-presenting cells (eg, DCs) for tumor-derived immune response. Meanwhile, the Wpep peptide worked as an immune adjuvant to provoke innate immune cells, such as DCs and natural killer (NK) cells, for cancer inhibition. Besides, the Wpep peptide could specifically bind to formyl peptide receptors, which are overexpressed in cancer cells. From this tumor-targeting delivery, the anticancer effects were enhanced precisely in local tumors. Compared with that from free oxaliplatin, the tumor sizes in the mice treated with the dual-functional nanoparticles showed a more than three-fold decrease in both MDA-MB-231 and 4T1 breast cancer models.

Immunotherapy through agonists can activate immune signaling pathways that promote adaptive immune response for cancer treatment. The combination of a Pt drug with a toll-like receptor 9 (TLR9) agonist through nanoparticles was reported by Huang’s group. Lipid bilayer-coated cisplatin nanoparticles (LPC) and liposomes encapsulated with unmethylated cytosine-phosphorothioate-guanine oligodeoxynucleotide (CpG-Lipo) were prepared. The combinatorial therapy was carried out by injection of LPC and CpG-Lipo in a B16F10 melanoma mouse model. After treatment, the antigen was generated in situ by the cytotoxic agent LPC. Simultaneously, the host immune response was subsequently activated by CpG, a well-known TLR9 agonist, to stimulate CTL. A strong synergistic antitumor effect has been observed in the treated mice.

containing DSCP and IDO inhibitor. (G) Measurement of T-cell proliferation after being cultured with different complexes for 6 days. (H) The growth of HeLa tumors in the xenograft model after treated with various groups. (I) Schematic of the simple self-assembly procedure used to prepare the Pt(IV)-IONP micelles and poly(I:C)-Pt(IV)-IONP micelles. (J) Flow cytometry assay to test the maturated DCs. (K) The components of therapeutic nanoparticles (TNPs). (L) TNPs were intravenously injected and imaged in real time within the tumor through a dorsal window chamber for pharmacokinetic and pharmacodynamic analysis. (M) Single-cell suspensions of the bulk tumor mass were gated and quantified according to the cell type. (N) Tumor inhibition of TNPs mediated with macrophages.
been achieved in the combinatorial therapy; the median lifespan was 45 days, which was significantly prolonged compared with 36-41 days for the monotherapies. Such combination induced more than four times of splenic interferon-γ (IFN-γ) production than the monotherapies. Since IFN-γ was produced by CTL, the increase of IFN-γ level indicated the existence of a high amount of CTL, which was also activated to “kill” cancer cells. The administration of CpG-Lipo plus LPC stimulated memory T cells as tumor vaccination in a tumor rechallenge test. Reduction of tumor metastasis and negligible toxicities were observed in this combinatorial therapy.

In the tumor microenvironment, cytokines also play vital roles in tumor suppression, and they act in each step in the cancer immunity cycle. Cytokines work as cancer immunotherapy by increasing effector immune cells and enhance their cytolytic activity in the TME. A strategy to combine Pt drug and cytokine has been considered to obtain more efficient tumor inhibition. However, intravenous injection of free Pt drug and cytokine may cause many side effects, such as cytokine storm. To this end, a local delivery system to combine Pt drug and cytokine was reported by Chen’s group. They prepared in situ-forming thermosensitive hydrogels containing cisplatin and interleukin-15 (IL-15) for melanoma treatment. Gradual degradation of the hydrogels was observed by subcutaneous injection in the back of rats. The sustained release of drugs from the injected hydrogels was detected until 3 weeks later. Consequently, the tumor volume in the group treated with the hydrogels decreased about 88% than that from free IL-15 and cisplatin, suggesting the synergistic anticancer effect of the designed nanosystem. The results were owing to a combination of cisplatin-mediated S phase arrest and IL-15-induced recovery of CD8+ T and NK cells. Besides, the peritumoral injection of the hydrogels could help to reduce the systematic adverse effects.

Nanoparticles containing Pt drugs can be employed to enhance cancer treatment by activating the immune system; they can also be delivered to the TME through the help of macrophage. Weissleder et al established therapeutic nanoparticles (TNPs) to monitor DNA damage in real-time in vivo at the single-cell level (Figure 6K and L). TNPs consist of three components, including a boron-dipyrromethene (BODIPY)-conjugated cisplatin prodrug as the cytotoxic drug payload, a BODIPY630-conjugated poly(D,L-lactic-co-glycolic acid) (PLGA) as the TNP vehicle, and a clinically tested polymer PLGA-b-PEG as the core and shell of the nanoparticles. Compared with the unencapsulated Pt drugs, TNPs exhibited a fivefold increased blood circulation half-life in an in vivo model. Unexpectedly, cancer treatment by TNPs was achieved with the help of tumor-associated macrophage (TAM). Although TAM only comprised 4% of the total tumor mass, more than 40% of the total administrated TNPs were detected in TAMs (Figure 6M). Consequently, the TNPs were gradually transferred from the “drug depot” TAMs to neighboring tumor cells, resulting in further enhancement of DNA damage (Figure 6N). The TAM-mediated drug delivery also helped to block the development of local metastases.

It is clear that the applications of cytotoxic Pt-based chemotherapeutics provide additional therapeutic benefits to potentiate anticancer immune response. Based on the reports mentioned above and those not included in this review, the combination of Pt-based chemotherapy and immunotherapy using nanomaterials is an effective strategy for future cancer treatment, especially in drug-resistant cancers and those with low immune response. Using the nanodelivery systems, the chemo-immunoregimens can exert anticancer activity more efficiently with less systematic side effects than the conventional monotherapies.

6 | CONCLUSION AND PERSPECTIVE

In this review, we summarized the most recent development of Pt drug-based combinatorial therapeutic strategies delivered by nanovehicles. Representative examples in each category were discussed with a focus on their design, mechanism of action, and anticancer effects. Compared with monotherapies or the simple combination of free drugs, these nanocarrier-based combinatorial therapies afford increased synergistic effects, improved pharmacokinetic properties, decreased side effects, and enhanced anticancer efficacy.

Inspiring anticancer efficiency has been observed for these nanomaterial-mediated combinatorial therapies in the preclinical studies, highlighting their great potential for cancer treatment. Each combinatorial treatment, however, has its unique advantages and limitations. For instance, combining Pt drugs with other chemotherapeutic drugs is applicable to a wide type of cancers, which augments the anticancer spectrum of platinum drugs, but its further application is limited by various side effects. Combining with Pt drugs is a practical way to improve the effectiveness of conventional PDT agents against hypoxia tumor microenvironment; in return, PDT agents could overcome the drug resistance of cancer cells toward Pt drugs. For Pt drug-PTT combination, the heat generated by PTT agents facilitates the accumulation of Pt drugs in cancer cells via enhancement of membrane permeability, and Pt drugs could amplify the DNA damage signals induced by PTT agents. Therefore, the combination of PDT/PTT with platinum drugs has achieved superior anticancer effects. In several examples mentioned in this
review, the tumors were completely ablated, and no tumor recurrence was observed. Nevertheless, the efficiency of PDT/PTT is limited by the low tissue penetration depth of light. Thus, PDT/PTT is only applicable to superficial tumors. The combination of Pt with immunotherapy via nanocarriers can broaden the treatment range of cancer types and enhance the cancer treatment efficacy in those patients with a low response rate toward immunotherapy alone. Owing to the long-term immunological memory response, immunotherapy will achieve sustained inhibition of the proliferation of cancer cells, which will prolong the survival time. Compared with other combinatorial therapies involving Pt drugs, the combination of Pt drugs with immunotherapeutic agents possesses higher anticancer efficiency, fewer side effects, and a lower possibility for cancer relapse. Therefore, the combination has been regarded as a promising cancer treatment strategy, although further improvement to enhance the response rate and decrease the side effects is still highly desired.

Finally, recent studies have suggested that Pt-based drugs do not function only as DNA-damaging agents but they also possess several unique properties that may be exploited in nanomedicine. For example, a moderate dose of cisplatin was found to generate an immune-enhancing effect toward anti-PD-L1/PD-1 immunotherapy, which is favorable for combinatorial therapy with PD-L1 checkpoint inhibitors. In another example, oxaliplatin was found to be a ribosome biogenesis stress inducer, and thus coloading nanoparticles with oxaliplatin and other agents that target the protein homeostasis network may enable the treatment of cancer stem cells or metastatic tumor cells that are resistant to chemotherapy. In conclusion, the rapid development of nanomaterials provides a promising platform for combinatorial drug delivery. The development of stable and multifunctional nanodelivery systems will certainly improve the therapeutic efficacy of Pt-based combinatorial treatments, and expand the breadth of their potential applications in the clinic.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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