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Review Article

Advances, Challenges, and Future Perspectives in the Detection and Quantification of Platinum Levels in Chemotherapy Patients

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Abstract

Platinum-based chemotherapeutic agents remain among the most effective and widely used drugs in cancer treatment. Since the clinical introduction of cisplatin, platinum complexes such as carboplatin and oxaliplatin have significantly improved therapeutic outcomes in several malignancies, which include testicular, ovarian, colorectal, lung, and bladder cancers. In spite of their remarkable clinical success, the therapeutic application of platinum drugs is frequently limited by severe toxicities, drug resistance, poor selectivity, and interpatient variability in pharmacokinetics. Consequently, accurate monitoring of platinum concentrations in biological systems has become increasingly important for optimizing dosage regimens, minimizing adverse effects, and improving therapeutic efficacy. This review discusses recent advances in the detection and quantification of platinum species in human samples, with emphasis on analytical and imaging techniques employed in clinical and biomedical studies. Conventional approaches such as graphite furnace atomic absorption spectroscopy (GF-AAS), inductively coupled plasma mass spectrometry (ICP-MS), high-performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), and X-ray absorption spectroscopy are critically examined alongside emerging technologies including fluorescence probes, biosensors, electrochemical sensing platforms, and nanotechnology-assisted imaging systems. The review further highlights the role of intracellular platinum tracking, mitochondrial targeting, and single-cell analysis in understanding platinum drug metabolism and mechanisms of resistance. Current challenges and future prospects in platinum monitoring for precision oncology are also discussed.

Keywords: Platinum-based chemotherapy, cisplatin monitoring, biosensors, drug resistance, precision oncology.

1. INTRODUCTION

Platinum coordination complexes represent a cornerstone of modern anticancer therapy. The serendipitous discovery of cisplatin's antiproliferative properties by Rosenberg *et al.,* in the 1960s revolutionized the treatment of metastatic cancers (Rosenberg, VanCamp, & Krigas, 1965). Today, platinum agents are first-line treatments for testicular, ovarian, colorectal, non-small cell lung, and bladder malignancies (Kelland, 2007; Wheate, Walker, Craig, & Oun, 2010).

However, the narrow therapeutic index of platinum drugs remains a major clinical challenge. Nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression frequently necessitate dose reduction or treatment discontinuation (Miller, Tadagavadi, Ramesh, & Reeves, 2010). Moreover, intrinsic or acquired resistance develops in the majority of patients with advanced disease, driven by mechanisms such as reduced drug uptake, increased inactivation by glutathione and metallothioneins, and enhanced DNA repair (Galluzzi *et al.,* 2012; Amable, 2016).

Significant interpatient variability in platinum pharmacokinetics further complicates dosing. Body surface area (BSA)-based dosing, while standard, fails to account for renal function, albumin levels, and genetic polymorphisms in drug transporters (de Jongh *et al.,* 2003; Urien & Lokiec, 2004). Therefore, therapeutic drug monitoring (TDM) of platinum levels is increasingly recognized as a critical tool for personalized chemotherapy.

This presented review provides an update on analytical methods for platinum detection and quantification, compares their clinical utility, and outlines emerging technologies that could transform precision oncology.

2. Conventional Analytical Techniques for Platinum Quantification

2.1 Graphite Furnace Atomic Absorption Spectroscopy (GF-AAS)

GF-AAS has been widely used for decades due to its high sensitivity for platinum (detection limits of 0.5–5 µg/L) and relatively low operational cost (Morrison, 1991). The technique measures ground-state platinum atoms after electrothermal atomization. GF-AAS has been successfully applied to monitor plasma and urine platinum levels in patients receiving cisplatin and carboplatin (Pereira, de Sá, & de Oliveira, 2019).

However, GF-AAS requires large sample volumes, is time-consuming, and cannot distinguish between different platinum species (e.g., intact drug vs. protein-bound metabolites). This limitation is significant, as only unbound platinum is pharmacologically active (Hanna & Pearson, 2019).

2.2 Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

ICP-MS has become the gold standard for total platinum quantification in biological matrices. It offers exceptional sensitivity (detection limits as low as 0.01 µg/L), wide linear dynamic range, and multi-element capability (Brouwers, de Jong, & Huitema, 2008). Brouwers *et al.,* (2008) validated an ICP-MS method for cisplatin, carboplatin, and oxaliplatin in human plasma ultrafiltrate, achieving accuracy within 96–105%.

ICP-MS is routinely used in pharmacokinetic studies to determine area-under-the-curve (AUC) and to guide carboplatin dosing using the Calvert formula (Calvert *et al.,* 1989). Nevertheless, ICP-MS cannot discriminate between parent drugs and inactive platinum adducts unless coupled with separation techniques.

2.3 High-Performance Liquid Chromatography (HPLC)

HPLC enables speciation analysis by separating platinum-containing species prior to detection. When coupled with UV–Vis or mass spectrometry, HPLC allows simultaneous quantification of intact cisplatin, carboplatin, oxaliplatin, and their hydrolysis products (Hann *et al.,* 2003; Falta *et al.,* 2011). Hann *et al.,* (2003) reported baseline separation of cisplatin and its monohydrated complex using ion-pair chromatography.

The primary drawback of HPLC is lower sensitivity compared to ICP-MS and longer analysis times (typically 15–30 minutes per sample). Additionally, sample preparation must be rapid to prevent ex vivo biotransformation (Bell, McKeage, & Galettis, 2017).

2.4 Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR provides unique structural information on platinum-drug interactions without sample destruction. 1H1*H* and 195Pt195*Pt* NMR have been used to characterize cisplatin binding to DNA and glutathione (Bancroft, Lepre, & Lippard, 1990; El-Khateeb, Appleton, Gahan, Charles, & Berners-Price, 1999). However, low intrinsic sensitivity and high sample concentration requirements (typically >10 µM) preclude routine clinical TDM. 2D NMR techniques improve resolution but remain primarily a research tool.

2.5 X-ray Absorption Spectroscopy (XAS)

XAS, including X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS), reveals the oxidation state and coordination environment of platinum. Hall *et al.,* (2008) used XANES to demonstrate that intracellular platinum in cisplatin-resistant ovarian cancer cells remains predominantly in the +2 state, unlike sensitive cells where reduction to Pt(0) occurs. The major limitation is the need for synchrotron radiation facilities, making XAS impractical for routine clinical labs.

3. Emerging Technologies for Platinum Detection

3.1 Fluorescence Probes and Imaging Reagents

Fluorescent chemosensors offer real-time, non-invasive platinum tracking in living cells. The first small-molecule fluorescent probe for cisplatin, PtCy5, was developed by Shen *et al.,* (2015) and enables imaging of platinum accumulation in perinuclear regions. More recently, aggregation-induced emission (AIE)-based probes have improved signal-to-noise ratios (Chen *et al.,* 2018). These probes are valuable for high-content screening but have not yet been validated in patient samples.

3.2 Electrochemical Biosensors

Electrochemical sensors provide rapid, low-cost, and portable detection. Carbon nanotube- and graphene-based electrodes modified with platinum-specific ligands or aptamers have achieved detection limits for cisplatin as low as 0.5 nM (Bagheri, Rezvani, & Naderi, 2020). An aptasensor developed by Asadian *et al.,* (2019) showed linear response from 1 to 100 nM and was successfully applied to spiked human serum. Key challenges include surface fouling by proteins and lack of multiplexing capability.

3.3 Nanotechnology-Assisted Systems

Nanoparticle-enhanced assays combine the sensitivity of noble metal nanostructures with selective recognition elements. Gold nanoparticles (AuNPs) functionalized with platinum-binding peptides enable colorimetric detection visible to the naked eye (Wu *et al.,* 2017). Similarly, quantum dot-based fluorescence resonance energy transfer (FRET) sensors have been reported for oxaliplatin quantification (Li, Wang, & Lu, 2019). Clinical translation is hindered by batch-to-batch variability and regulatory hurdles.

4. Beyond Bulk Concentration: Cellular and Subcellular Platinum Tracking

4.1 Intracellular Tracking and Mitochondrial Targeting

Platinum accumulation in mitochondria contributes to apoptosis through reactive oxygen species (ROS) generation and opening of the mitochondrial permeability transition pore (Marullo *et al.,* 2013). Using ICP-MS of isolated organelles, we now know that mitochondrial platinum levels correlate better with cytotoxicity than nuclear platinum in some cell lines (Cullen, Yang, & Wang, 2007). Mitochondria-targeted platinum (IV) prodrugs are being designed to exploit this vulnerability (Wang *et al.,* 2020).

4.2 Single-Cell Analysis

Bulk measurements mask cellular heterogeneity. Single-cell ICP-MS (sc-ICP-MS) allows quantitation of platinum distribution across individual cells. Meyer *et al.,* (2018) demonstrated that only 20% of cells in a cisplatin-treated population accumulate lethal platinum doses, with the remainder exhibiting a "drug-tolerant persister" phenotype. This technique has enormous potential for understanding resistance emergence.

5. Platinum Metabolism and Mechanisms of Resistance

Monitoring platinum levels directly informs resistance mechanisms. Reduced intracellular platinum is observed in many resistant lines due to downregulation of copper transporter CTR1 (Ishida, Lee, & Thiele, 2002) and upregulation of ATP7A/ATP7B efflux pumps (Samimi *et al.,* 2004). Increased sequestration by glutathione (GSH) and metallothioneins also reduces bioavailable platinum (Godwin, Schold, & Frei, 1992). Emerging techniques such as laser ablation-ICP-MS (LA-ICP-MS) can map platinum distribution in tumor biopsies, revealing heterogeneous accumulation patterns (Moreno-Gordaliza *et al.,* 2010).

6. Current Challenges

In spite of the technical advances but there are several obstacles as follow:

Lack of speciation in routine TDM: Total platinum does not equal active drug. Clinical labs rarely separate free from bound platinum.

Sample stability: Platinum complexes hydrolyze or bind to proteins ex vivo if not processed immediately (Bell *et al.,* 2017).

Standardization: No certified reference materials for platinum species in plasma exist. Inter-laboratory variability is high.

Cost and accessibility: ICP-MS and NMR require expensive infrastructure. GF-AAS is cheaper but labor-intensive

Invasive sampling: Most methods require blood or urine. Non-invasive monitoring (e.g., sweat, breath) remains experimental.

7. Future Perspectives

The future of Oncopharmacology will likely involve the routine integration of platinum monitoring through:

1. Microfluidic lab-on-a-chip devices that couple plasma separation with electrochemical detection for point-of-care TDM (Wang & Lin, 2021).
2. Machine learning models integrating patient genetics, renal function, and real-time platinum levels to predict toxicity and efficacy (Lü *et al.,* 2020).
3. Theranostic nanoparticles that simultaneously deliver platinum prodrugs and enable photoacoustic or MRI-based tracking (Miller *et al.,* 2021).
4. Standardization initiatives led by the International Union of Pure and Applied Chemistry (IUPAC) for platinum speciation reference materials.

8. CONCLUSIONS

Accurate detection and quantification of platinum levels in chemotherapy patients is essential for maximizing efficacy while minimizing toxicity. While GF-AAS and ICP-MS remain the clinical workhorses for total platinum measurement, speciation methods (HPLC-ICP-MS) and emerging biosensors promise richer pharmacokinetic data. The integration of single-cell and subcellular techniques will deepen our understanding of resistance. Overcoming standardization, cost, and speciation barriers will enable precision TDM for platinum-based chemotherapy, ultimately improving outcomes for millions of cancer patients worldwide.

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