

Review

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Review

High-Frequency Pharmacologic Ascorbate Therapy for Cancer: A Dual-Pulse Oxidative Stress Strategy (DP-HDIVC) Targeting Tumor Redox Vulnerability

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Abstract

High-dose intravenous vitamin C (HDIVC) has been investigated for decades as a potential anticancer therapy based on its ability to achieve pharmacologic plasma concentrations that exert pro-oxidative cytotoxic effects selectively in cancer cells. While prior clinical and translational studies have focused primarily on dose escalation and safety, **infusion frequency has remained underexplored as a determinant of anticancer efficacy**. Accumulating mechanistic evidence indicates that cancer cell killing by pharmacologic ascorbate depends not only on peak plasma concentration (C_{max}), but also on the **frequency of suprathreshold oxidative stress exposure and the tumor's limited capacity for redox recovery**. Here, we propose a **high-frequency, dual-pulse HDIVC strategy**, consisting of once- or twice-daily pharmacologic infusions designed to repeatedly exceed cytotoxic plasma thresholds, thereby reducing tumor redox recovery time and amplifying cumulative oxidative injury. This framework explicitly distinguishes **metabolic redox suppression dosing** from **high-peak cytotoxic pulse dosing**, imposes strict temporal separation from antioxidant/reductive therapies, and is optimized for implementation in patients with central venous access under appropriate clinical monitoring. We argue that **frequency-intensified pharmacologic ascorbate exposure represents a rational next step for maximizing cancer cell kill**, meriting formal clinical evaluation. This manuscript presents a mechanistic and conceptual framework intended to guide protocol design and stimulate formal clinical evaluation, rather than to report completed clinical outcomes.

Keywords: high-dose intravenous vitamin C; pharmacologic ascorbate; cancer therapy; oxidative stress; redox biology; hydrogen peroxide; tumor redox vulnerability; redox adaptation; oxidative cytotoxicity; infusion frequency; dual-pulse dosing; pharmacokinetics; temporal redox partitioning

1. Introduction

Intravenous vitamin C achieves plasma concentrations several orders of magnitude higher than oral administration, enabling pharmacologic effects not achievable through nutritional supplementation. At sufficiently high concentrations, ascorbate functions as a **pro-oxidant**, generating extracellular hydrogen peroxide (H_2O_2) that induces selective oxidative stress in cancer cells with impaired antioxidant defenses, while sparing normal tissues[1,2].

Despite extensive mechanistic and early clinical research, clinical application of HDIVC remains heterogeneous, with most protocols emphasizing **dose magnitude** (e.g., 1–1.5 g/kg) and **weekly frequency (2–3×/week)**. However, this approach implicitly assumes that **single large oxidative insults** are sufficient for sustained tumor control—an assumption increasingly at odds with modern understanding of tumor redox adaptation and metabolic resilience.

Historically, HDIVC has most commonly been administered two to three times weekly, a schedule largely driven by clinical practicality, outpatient feasibility, and early safety considerations. These regimens were not specifically designed to optimize the frequency of pharmacologic oxidative

stress exposure or to account for tumor redox recovery dynamics, which may be critical determinants of cancer cell killing.

Accordingly, a frequency- and timing-based framework grounded in tumor redox biology may provide a more rational basis for protocol optimization.

2. Rationale for High-Frequency Oxidative Stress in Cancer Therapy

2.1. Cancer Redox Recovery as a Therapeutic Limitation

Cancer cells exhibit altered redox homeostasis and heightened basal oxidative stress, rendering them vulnerable to further oxidative insults. However, they also possess inducible antioxidant systems that enable partial recovery following transient oxidative exposure. When oxidative stress is delivered infrequently, surviving tumor cells may adapt and repopulate between treatments.

Experimental evidence suggests that repeated suprathreshold oxidative hits, delivered before full redox recovery can occur, are more likely to produce irreversible cellular damage than isolated high-dose exposures[3,4].

This strategy leverages the differential redox buffering capacity between malignant and normal tissues, with host recovery supported during non-oxidative windows.

2.2. Pharmacologic Ascorbate as a Repeated Oxidative Pulse Generator

Pharmacologic concentrations of ascorbate (≥15–20 mM plasma) generate extracellular H₂O₂ in the tumor microenvironment. The **cytotoxic event is time-limited**, corresponding to the presence of high plasma ascorbate levels. Therefore, **the number of times this threshold is exceeded** may be as important as the absolute peak achieved.

This observation leads to a key hypothesis:

Cancer cell killing by HDIVC is optimized by increasing the frequency of suprathreshold oxidative pulses, not merely by maximizing single-dose exposure.

3. Conceptual Framework: The Dual-Pulse High-Frequency HDIVC Model

The proposed framework introduces a **frequency-intensified, dual-pulse strategy**, consisting of:

3.1. Daily Metabolic Suppression Dosing

- **Purpose:** Maintain persistent oxidative and metabolic pressure within the tumor microenvironment
- **Dose range:** ~0.75–1.0 g/kg per infusion
- **Frequency:** Once daily (baseline) or twice daily (intensified phase)
- **Infusion duration:** 60–120 minutes

This component aims to **limit tumor redox recovery**, weaken antioxidant buffering capacity, and sensitize cancer cells to subsequent cytotoxic insults.

3.2. High-Peak Cytotoxic Pulse Dosing

- **Purpose:** Deliver discrete, maximal oxidative killing events
- **Dose range:** 1.25–1.5 g/kg (NIH-established upper safety range)
- **Frequency:** 1–2 non-consecutive days per week
- **Infusion duration:** 45–75 minutes to maximize C_{max}

These pulse infusions are designed to generate **unpredictable, high-amplitude oxidative stress**, exceeding the adaptive capacity of tumor cells.

Together, these layers form a **high-frequency oxidative assault strategy**, rather than a static maintenance therapy.

This dual-pulse model is intended as a flexible, hypothesis-driven framework rather than a rigid dosing mandate, allowing adaptation based on tumor type, patient tolerance, and pharmacokinetic considerations.

4. Temporal Redox Partitioning: Avoiding Antioxidant Interference

A critical and often overlooked factor in HDIVC therapy is the **timing of antioxidant or reductive interventions**. Concurrent administration of thiol-based antioxidants (e.g., glutathione, NAC) during the HDIVC oxidative window may blunt cytotoxic efficacy.

The proposed framework therefore mandates **strict temporal redox partitioning**:

- **Oxidative window (HDIVC infusion $\pm$ several hours):**

Pro-oxidative intent; antioxidant boluses avoided

- **Recovery window (non-infusion periods):**

Host-directed antioxidant and reparative support

This timing-based strategy allows **maximal cancer cell injury** while preserving host tissue resilience.

5. Clinical Implementation Considerations

High-frequency HDIVC is most feasible in patients with:

- Central venous access (e.g., PICC or port)
- Adequate renal function
- Normal G6PD activity
- Capacity for close laboratory and clinical monitoring

Safety data from prior Phase I and early clinical studies demonstrate that HDIVC up to 1.5 g/kg is generally well tolerated when appropriately screened and monitored[1].

6. Implications and Future Directions

This high-frequency, dual-pulse HDIVC framework reframes pharmacologic ascorbate therapy from a **dose-centric intervention** to a **frequency- and timing-optimized oxidative strategy**. It generates several testable predictions:

1. Twice-daily suprathreshold exposure will produce greater tumor control than equal total dose delivered less frequently
2. Shortened infusion durations during pulse days will increase C_{max} and cytotoxicity
3. Temporal separation from antioxidant therapy will enhance efficacy

Prospective pharmacokinetic, pharmacodynamic, and clinical outcome studies are required to validate these hypotheses.

7. Conclusions

More broadly, this approach aligns with systems-level models of cancer metabolism and redox biology, in which therapeutic efficacy depends on dynamic perturbation of adaptive tumor networks rather than static dose escalation alone.

High-dose intravenous vitamin C should be understood not as a nutritional supplement, but as a **pharmacologic oxidative therapy**. Maximizing anticancer efficacy likely depends on **how often cytotoxic plasma thresholds are exceeded**, not merely how high a single dose reaches. A high-frequency, dual-pulse HDIVC strategy offers a coherent, mechanistically grounded framework for maximizing cancer cell kill while maintaining safety, and provides a foundation for prospective clinical investigation.

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