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Gastric adenocarcinoma most often presents at an advanced stage and overall five-year survival of ~30%. Pharmacological ascorbate (high-dose IV ascorbate) has been proposed as a promising nontoxic adjuvant to standard radio-chemotherapies in several cancer types. In the current study, pharmacological ascorbate (0.5–2 m*M*) caused a dose-dependent decrease (70–85% at 2 m*M*) in clonogenic survival of gastric adenocarcinoma cells (AGS and MNK-45), but was relatively nontoxic to a small intestinal epithelial non-immortalized human cell isolate (FHs 74 Int). The addition of pharmacological ascorbate (1 m*M*) to standard radio-chemotherapies [i.e., 5-FU (5 μ*M*); cisplatin (0.5 μ*M*); irinotecan (2.5 μ*M*); carboplatin (5 μ*M*); paclitaxel (2–4 n*M*); and X rays (1.8 Gy)] also potentiated gastric cancer clonogenic cell killing [additional decreases were noted with: ascorbate plus 5-FU/radiation (1%); ascorbate plus cisplatin/irinotecan (9–19%); and ascorbate plus paclitaxel/carboplatin (6–7%)]. The gastric cancer cell toxicity and chemosensitization seen with pharmacological ascorbate was dependent on H_2O_2 and the presence of catalytic metal ions. In addition, pharmacological ascorbate dosing resulted in a concentration-dependent decrease (64% at 20 m*M*, $P \leq 0.0001$) in cancer cell invasion and migration that was inhibited by catalase. Finally, pharmacological ascorbate significantly increased the overall survival of mice with gastric cancer xenografts when used in combination with paclitaxel, carboplatin and radiation ($P = 0.019$). These results demonstrate that pharmacological ascorbate is selectively cytotoxic to gastric adenocarcinoma cells (relative to normal intestinal epithelial cells) by a mechanism involving H_2O_2 and redox active metal ions. Furthermore, pharmacological ascorbate significantly enhances gastric cancer xenograft responses to radio-chemotherapy as well as inhibiting tumor cell migration and invasiveness. Overall, these results support the hypothesis that pharmacological ascorbate can be used as an adjuvant with standard-of-care radio-chemotherapies for the treatment of gastric adenocarcinomas.

INTRODUCTION

Gastric adenocarcinoma (GAC) is a highly lethal disease due to treatment resistance and a propensity for metastasis. GAC is currently the fourth leading cause of cancer-related deaths worldwide and the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database estimates 28,000 new cases in the U.S. for 2017 (*1*). The overall five-year relative survival rate of patients with GAC in the U.S. is approximately 30%, with a median survival of only 12 months (*1, 2*). The reason for this dismal survival rate is that most stomach cancers are diagnosed at an advanced stage or after distant metastases have formed, impacting patient prognosis. Treatment options for GAC vary by stage and include combinations of multimodality treatments, such as surgery, chemotherapy (neoadjuvant and adjuvant), radiation therapy, radio-chemotherapy and potentially targeted therapy.

In 1976, it was suggested by Cameron and Pauling that ascorbate, given both orally and intravenously at a high dose (pharmacological ascorbate), could be used as a potential anti-cancer therapy (*3*). Shortly after this suggestion, two separate clinical trials failed to show efficacy of ascorbate on patient survival (*4, 5*). However, these trials used high-dose oral ascorbate without the addition of intravenous ascorbate. At physiologic concentrations (plasma levels 50–90 μ*M*), ascorbate (vitamin C) is well known as an effective reducing agent and antioxidant (*6*). Interestingly, at pharmacological levels (~10–20 m*M*), ascorbate can also act as a pro-oxidant that generates increased levels of hydrogen peroxide (H_2O_2) (*7–13*). It does so by increasing the steady-state concentration of H_2O_2 [(reactive oxygen species (ROS)] in the presence of

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