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Research Paper

Vinorelbine Potently Induces Placental Cell Death, Does Not Harm Fertility and is a Potential Treatment for Ectopic Pregnancy

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ABSTRACT

Ectopic pregnancies complicate 1–2 pregnancies and are a leading cause of maternal death. An effective oral drug therapy that replaces surgery might make its treatment safer, cheaper, simpler and therefore more widely accessible. The only current medical treatment offered to women is intramuscular methotrexate, but this only reliably resolves smaller ectopic pregnancies. As such, many ectopic pregnancies require surgical excision. We show that vinorelbine, an orally available chemotherapeutic agent, potently induced placental cell death but did not harm fertility in mice. Vinorelbine was 100–1000 times more potent than methotrexate in inducing placental cell death in vitro, and more potent than combination methotrexate and gefitinib (another proposed treatment for ectopic pregnancy being evaluated in phase III trials). Mechanistically, it caused microtubule condensation, blocked mitosis and activated the apoptosis cascade in placental cells. Vinorelbine was more efficacious than methotrexate ± gefitinib in reducing the volume of placental cell tumors xenografted subcutaneously in SCID mice. Mice exposed to vinorelbine and allowed to breed, following a four week washout period, displayed normal fertility, however long-term fertility was not assessed. Human Fallopian tubes treated with vinorelbine did not exhibit up-regulation of apoptosis molecules. Our findings show that placental cells appear sensitive to vinorelbine and it has potential as a tablet-only approach to treat ectopic pregnancy.

1. Introduction

Ectopic pregnancies arise when a conceptus implants outside the uterine cavity, with over 98% implanting in the Fallopian tube (Bouyer et al., 2002). They are life-threatening as they can erode through maternal vessels and cause fatal bleeding (Knight et al., 2016) and are one of the main causes of maternal death during the first trimester. They are also common, complicating 1–2% of all pregnancies with around 100,000 cases diagnosed each year in the United States alone (Centre for Disease Control and Prevention, 1995).

Many are treated surgically (Jurkovic and Wilkinson, 2011) where often, the entire Fallopian tube is removed together with the ectopic pregnancy. A simple and highly efficacious medical option could make the treatment of ectopic pregnancy safer (avoiding the risks of surgery), simpler (requiring less highly trained staff) and cheaper. The further implications are that the treatment could become more accessible in resource poor settings where surgery is either difficult to access, or not available.

There is one medical treatment offered clinically instead of surgery, intramuscular methotrexate (RCOG, 2016; The ACOG Task Force, 2008). However, methotrexate is only efficacious for smaller ectopic pregnancies that fulfill strict clinical criteria, and its rates of failure are too high for larger ectopic pregnancies (which will then often require salvage surgery) (RCOG, 2016). Furthermore, it often takes approximately one month for the ectopic pregnancy to resolve following methotrexate management (Skubisz et al., 2013) and, owing to its limited effectiveness, is less cost effective than laparoscopic (surgical) excision(Mol et al., 2008). Consequently, many ectopic pregnancies are surgically excised (Jurkovic and Wilkinson, 2011).

We previously identified the possibility that adding gefitinib tablets (an epidermal growth factor inhibitor that adversely affects placental signaling to cause apoptosis) to the intramuscular methotrexate might

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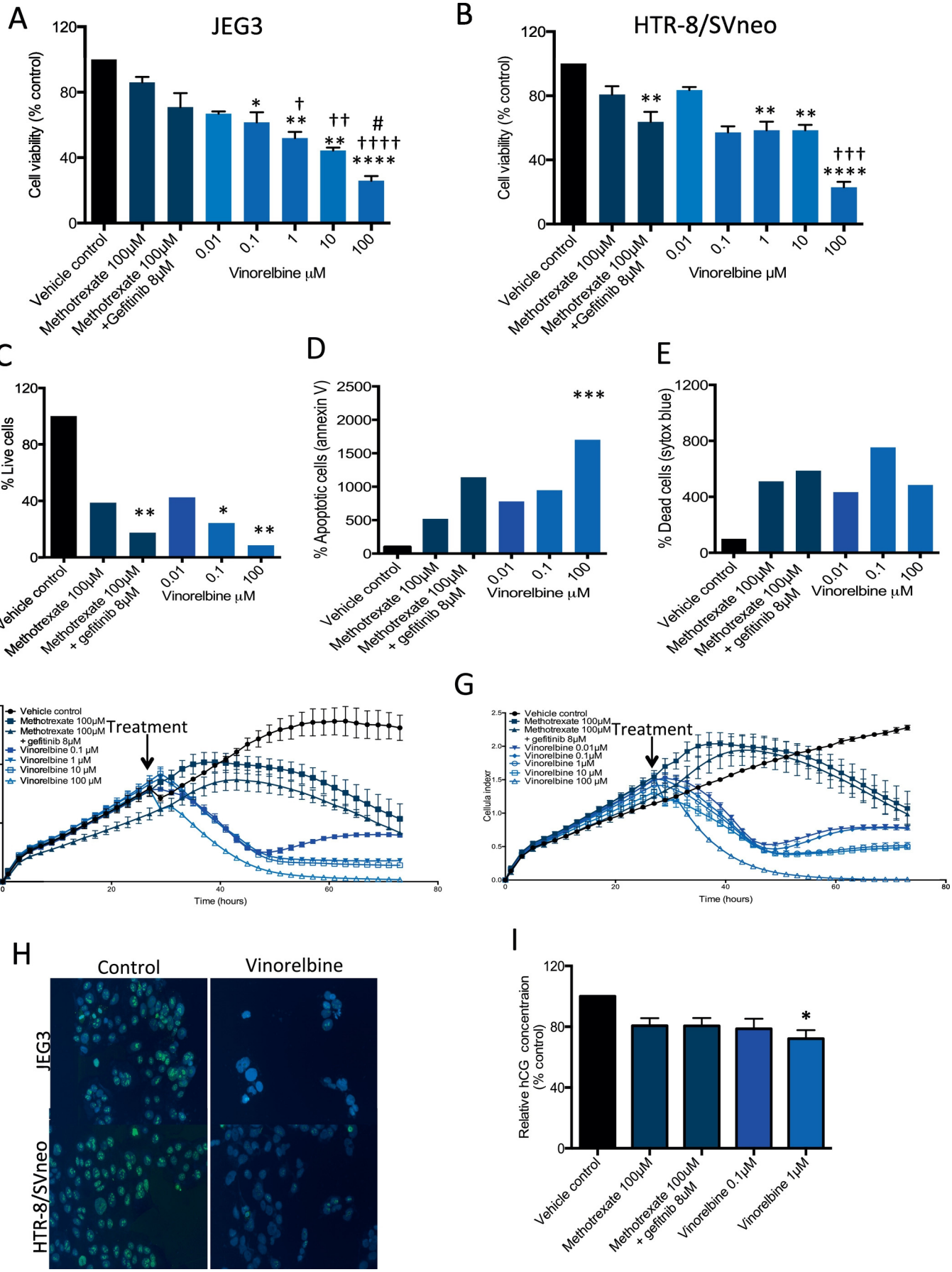

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