Are iron deficiency and peripheral neuropathy from oxaliplatin linked ?

A consumer-driven research idea with a plausible biological hypothesis (we think).

We encourage you to consider the possibility that iron deficiency (not only anaemia) may worsen CIPN.

THE ORIGINS OF THIS IDEA

- ❑ **A CIPN sufferer found a paper (1) associating oxaliplatin-induced CIPN with iron deficiency anaemia.**
- ❑ **We looked for further evidence – we did not find similar findings in cancer, but there are papers describing peripheral neuropathy associated with iron deficiency in diabetic humans (2) and animals (3) and in anaemic adults (4) and children (5).**
- ❑ **These findings are supported by biochemical evidence:**
  - ➢ Iron is critical to DNA replication and repair (6) – a process severely impacted by oxaliplatin.
  - ➢ Iron is critical to the work of Schwann cells – which maintain myelin sheaths (7) and have a recently been found to have a role in nociception (8).
  - ➢ Ferrous Iron and Platinum are both transition elements and have an oxidation state of +2. They are transported by different mechanisms inside cells (9, 10) but Pt++ may impact Fe++ transport without itself being transported – no-one knows.
  - ➢ The role of iron in: maintaining a healthy PNS, and in DNA replication and repair in the PNS and elsewhere, are reasons to ensure iron levels are adequate, independent of the risk of increased CIPN via a lack of iron.
- ❑ **There seems ample opportunity for critical iron-dependent mechanisms, essential to the PNS, to be interfered with by platinum – surely worse if iron is scarce or unavailable.**
- ❑ **AGITG researchers are pursuing a retrospective analysis of available clinical data to see if it might justify a prospective trial.**

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- Peripheral neuropathy from chemo is **terrible!**
- There are no effective preventive or treatment strategies for chemotherapy induced peripheral neuropathy (CIPN).
- Consumers wish to see some progress and to be part of the solution not just 'the problem'.
- We propose an idea we feel is biologically plausible, with potential for future research.

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DETAILS SUPPORTING BIOLOGICAL PLAUSIBILITY

CLINICAL:

1. Vincenzi and others (2013) Found a significant association between peripheral neuropathy (PN) and iron deficiency anaemia (IDA) in a retrospective study of 169 CRC patients all treated with Adjuvant Folfox-4. The actual difference is not great however: Grade 2 - 3 toxicities in 56% of the anaemic patients (52/93) and 47% of the non-anaemic patients (36/76), p=0.001.
2. Wu et al (2017) found an association between iron deficiency and peripheral neuropathy, examining 1134 type 2 diabetes patients. Anaemia almost doubled the risk of diabetes-related peripheral neuropathy (odds ratio 1.9, p< 0.001). They concluded anaemia is an independent risk factor for PN in diabetics.
3. This study seems to be a one-off, but the supporting animal evidence is strong (e.g. Baum et al 2016; Paeschke et al, 2016)
4. Degirmenci & Kececi (2011) conducted electrophysiological (EP) assessments of 52 adult patients with newly diagnosed IDA, and in 30 age-matched healthy controls. Oral iron therapy fixed most patients.
5. Kabakus et al (2002) did EP studies on 18 anaemic children (aged 2 – 3 ½) & 12 controls. The anaemic children were given oral iron for 3 months. Conduction returned to normal after significant EP deficit in the children who were anaemic initially.

BIOCHEMICAL:

6. **DNA replication and repair is impeded** when Fe is low. Several critical pathways are dependent on adequate levels of iron (see e.g. reviews by Zhang, 2014, and Puig et al, 2017). When iron is scarce/not available there is a well-described failure in DNA replication and repair. Proteins that require iron as a co-factor include the three key DNA polymerases, as well as primases and helicases.
7. **The interaction of iron and the PNS** is described by Levi and Taveggia (2014), with many points where iron deficiency can affect the functioning of the PNS. These include: the dependence of Schwann cells on iron to myelinate the nerves of the PNS; AND a role of Fe^{++} and Fe^{+++} in producing reactive oxygen species, very harmful to the PNS.
   Levi and Taveggia list a range of conditions of differing aetiology involving the PNS in which iron disorders play a role, including Friedreich's ataxia, Restless leg syndrome, Charot-Marie-Tooth syndrome. They emphasise that while we know some of what happens there are many gaps in our understanding of the interaction of iron and the PNS.
8. **New nociceptive role for Schwann cells:** Very recently (August 2019) Abdo et al described a new type of Schwann cell that is directly involved in responding to harmful stimuli (nociceptive Schwann cells). If these are also iron-dependent, they may also play a role in CIPN.
9. **Intracellular iron transport** is controlled mainly by Divalent Metal Transporter 1 gene (DMT1), shown essential in maintenance of oligodendrites (Cheli et al, 2018) which are to the CNS what Schwann cells are to the PNS.
10. Platinum transport of cisplatin is controlled via the Copper Transporter 1 gene (CTR1). CTR1 knockout reduced cells' sensitivity to cisplatin (Ilyechova et al, 2019), but oxaliplatin is a little different, not relying only on CTR1.
    But could platinum from oxaliplatin, in its +2 form, interact with the DMT1 pathway in Schwann (or other) cells, decreasing iron transport into them, although not transported itself? No-one has looked at this.

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Abbreviations

AGITG: Australasian Gastro-Intestinal Trials Group
CIPN: Chemotherapy Induced Peripheral Neuropathy
CRC: Colorectal Cancer
DNA: Deoxyribonucleic acid
EP: Electrophysiological
Fe: Iron
Hb: Haemoglobin
PN: Peripheral neuropathy
PNS: Peripheral Nervous System
Pt: Platinum

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