Appendix 5: Mitigation of Harm from Fluorouracil

1. Mitigation of harm considerations specific to fluorouracil:

a. Probably useful
   i. Some sources recommend forced diuresis to improve fluorouracil elimination. While the effectiveness of this approach is not extensively documented, it is safe and prudent to admit such patients on parenteral hydration at a minimum of 2 litres per day.

   ii. An overdose of a fluorouracil with its potential myelotoxicity should be treated with myeloid growth factor support beginning at 24 hours after the incident or as soon as possible. Growth factor treatment reduces the likelihood of neutropenia and its infectious complications and has also been shown to reduce the risk of mucositis.

b. Possibly useful
   i. Oral glutamine supplements have been shown in a small randomized trial\(^14\) to reduce diarrhea and surrogates of gastrointestinal toxicity in the setting of high dose fluorouracil therapy. In the clinical trial, supplements were initiated prior to drug administration; however, there is no literature on the use of this strategy in a rescue setting. If used, these supplements should be begun promptly.

   ii. Cardiotoxicity is associated with high dose fluorouracil therapy, particularly when given in combination with cisplatin\(^15\), with short term electrocardiographic or biochemical evidence of ischemic change in more than 20% of patients. In the setting of fluorouracil overdose, baseline cardiogram and close cardiac monitoring are prudent.

   iii. A single randomized study\(^16\) of angiotensin converting enzyme therapy in patients who had been treated with high dose fluorouracil demonstrated reduced rates of development of cardiac dysfunction.

   iv. The literature on dialysis or hemoperfusion to remove fluorouracil is limited and inconclusive. Sauer et al\(^17\) report that the procedure is "possibly effective" in fluorouracil overdose, and Behesti et al\(^18\) report that, when used in a regional perfusion model, up to 85% of drug can be extracted by hemoperfusion over charcoal cartridges.


However, Keller et al\textsuperscript{19} state that hemoperfusion, hemofiltration and hemodialysis "cannot be guaranteed". Charcoal hemoperfusion is an uncommon procedure and would obviously require the involvement of a nephrologist with specialized training. Given the relatively short half-life of fluorouracil (6-20 minutes), this approach would have no usefulness unless initiated within hours after an overdose.

c. Experimental or ineffective:

i. A variety of agents have been reported in pre-clinical models to mitigate fluorouracil toxicity: hyaluronic acid, uridine, probucol, 5-benzylxoxybenzylbarbituric acid acyclonucleoside, 2,3,5-tri-0-acetyluridine, 5-phenylthioacyclouridine, and 5-phenylselenenyl-acyclouridine. Mechanisms to expedite and report the use of such agents in emergent clinical settings should be developed.

ii. Allopurinol ice balls have been used to prevent oral mucositis in patients receiving high dose fluorouracil, but two clinical trials\textsuperscript{20,21} have reported that systemic high dose allopurinol had no impact on fluorouracil toxicity.

\textsuperscript{21} Ahmann FR, Garewal H, Greenberg BR. Phase II trial of high-dose continuous infusion 5-fluorouracil with allopurinol modulation in colon cancer. Oncology. (1986) 43, 83-85.

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