Poster # P199

Apraglutide Treatment Reduces Chemotherapy-Induced Gastrointestinal (GI) Damage in Mice and Preserves Cellular Integrity During Chemotherapy

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INTRODUCTION

- Chemotherapy-induced mucositis is a common condition caused by the breakdown of the mucosal barrier.[1]
- Administration of exogenous glucagon-like peptide 2 (GLP-2) to rodents with chemically-induced enteritis has been associated with reduced epithelium damage and gut injury, decreased bacterial infection, and decreased mortality.
- GLP-2 decreases chemotherapy-induced mucositis via inhibition of apoptosis in the small and large intestine.
- Apraglutide is a potent GLP-2 receptor agonist specifically designed to have slower absorption, decreased clearance, increased resistance to proteolysis, and increased plasma protein binding compared with other GLP-2 analogs.[2]
- Apraglutide exhibits a trophic effect resulting in the increase of intestinal mucosal surface and weight in healthy animals.[3]
- The objective of these studies are to evaluate the efficacy of apraglutide in protecting the intestinal mucosa when administered as pre-treatment or concomitant treatment in models of chemotherapy-induced intestinal damage with cytarabine or melphalan.

METHODS

- The intestinoprotective effect of apraglutide was assessed in two mouse models of chemotherapy-induced GI damage
- In both models, mice that received vehicle-only without any treatment served as controls.
- Intestinal tissue histology, plasma citrulline, survival, and body weight were assessed in both models.

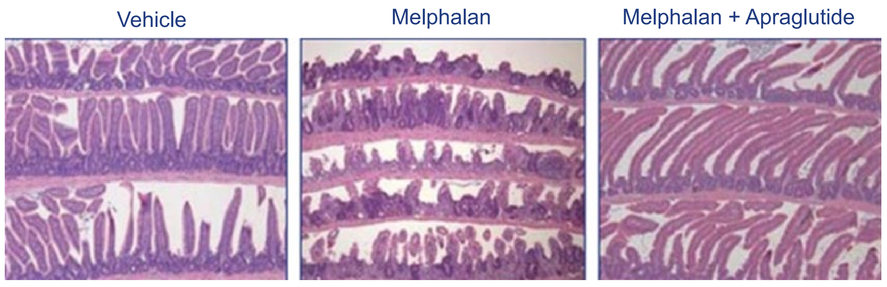
- Study 1 Included 4 groups of Balb/c mice:
  - A. Vehicle-only
  - B. Cytarabine (Days 0–4), no apraglutide
  - C. Cytarabine (Days 0–4) + concomitant apraglutide (Days 0–12)
  - D. Cytarabine (Days 0–4) + pre-treatment apraglutide (Days -4, -2) and continued as concomitant treatment (Days 0, +3, +6, +9 and +12)
  - – Cytarabine 30 mg/kg and apraglutide 1000 nmol/kg were used

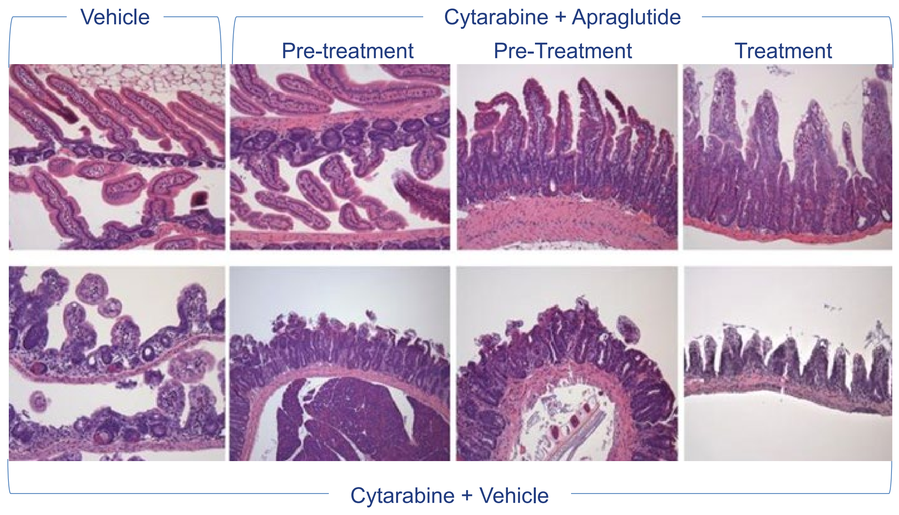
- Study 2 Included 3 treatment groups of Balb/c mice:
  - A. Vehicle-Only
  - B. Melphalan (Day 0), no apraglutide
  - C. Melphalan (Day 0) + pre-treatment apraglutide (Days -8, -6, -4, -4, -2) and continued as concomitant treatment (Days 0, +2, +4, and +6)
  - – Melphalan 17.5 mg/kg and apraglutide 3.3 mg/kg were used

RESULTS

Histological Examination

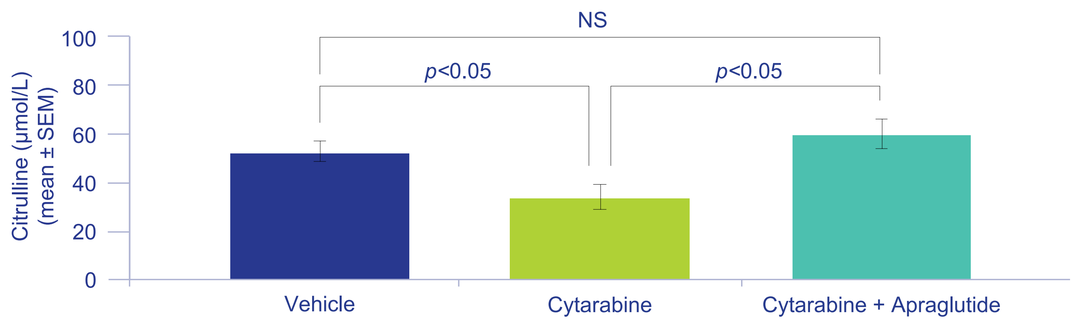
- Degenerative intestinal changes (villi and crypt atrophy) caused by cytarabine or melphalan were reduced by apraglutide co-administration, as demonstrated by similarities in tissue morphology between vehicle-treated and apraglutide-treated mice.
- The duodenum, ileum, and jejunum increased in weight when apraglutide was co-administered with cytarabine or melphalan.

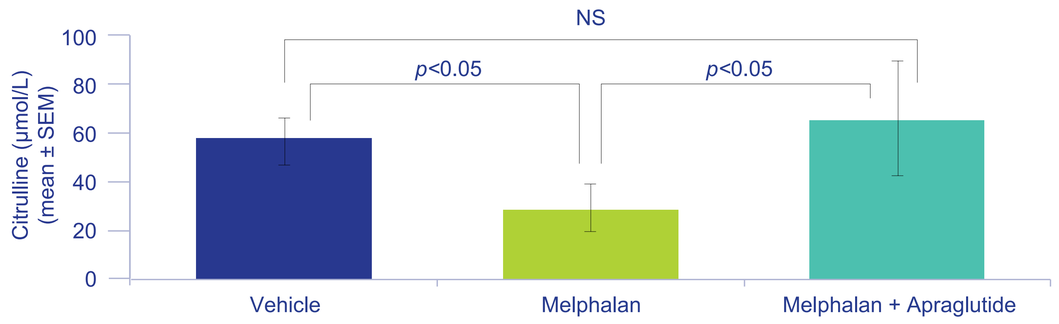




Plasma Citrulline Levels

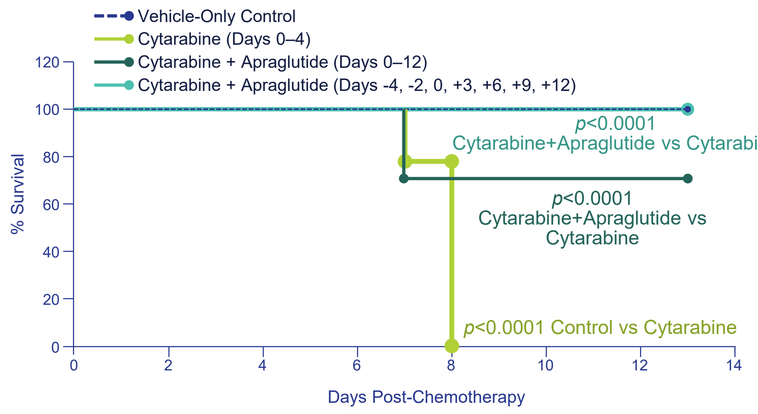
- The intestinal protective effects of apraglutide were supported by the preservation of plasma citrulline levels, a marker of mucosal mass and intestinal growth.
- Apraglutide-treated mice had similar plasma citrulline levels to mice that did not receive chemotherapy.

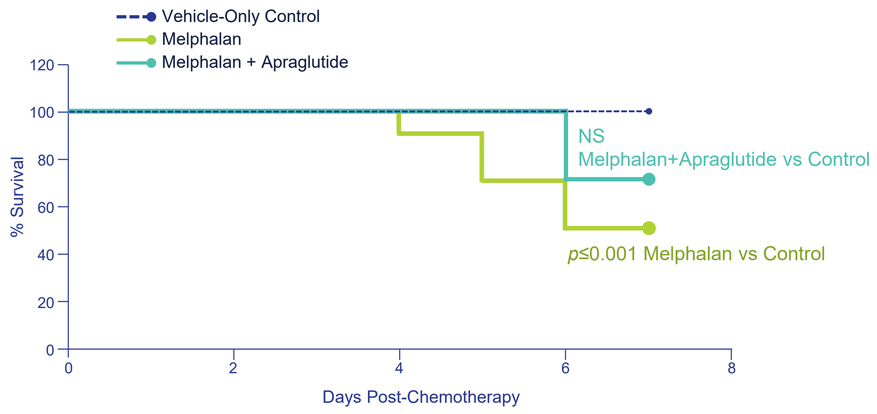


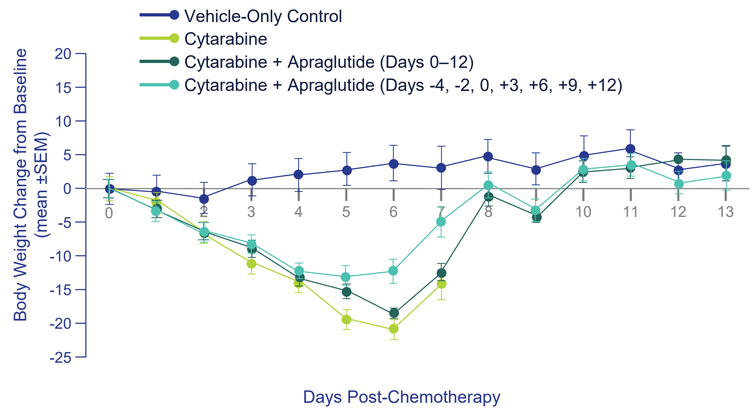


Survival and Body Weight

- Apraglutide attenuated chemotherapy-induced weight loss and improved overall survival vs. vehicle-only or chemotherapy-only groups.







CONCLUSION

- Cytarabine and melphalan are common chemotherapy agents used to treat acute leukemia as part of induction therapy or prior to allogeneic hematopoietic stem cell transplant (HSCT) and invariably induces degenerative intestinal changes (villi and crypt atrophy).
- Microscopic examination demonstrated the protective effect of apraglutide on the GI epithelium structure from chemotherapy- induced injury.
- Apraglutide prevented severe body weight loss, and improved survival in mice undergoing chemotherapy.
- Apraglutide also maintained plasma citrulline levels, a marker of intestinal mass, comparable to mice that did not undergo chemotherapy.
- The effects of apraglutide were optimal when it was administered as pre-treatment before chemotherapy.

REFERENCES

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3. Martchenko SE et al. Site-Specific and Temporal Effects of Apraglutide, a Novel Long-Acting Glucagon-Like Peptide-2 Receptor Agonist, on Intestinal Growth in Mice. J Pharmacol Exp Ther. 2020 Jun;373(3):347-352

DISCLOSURES

The study was sponsored by VectivBio and conducted in collaboration with the University of Toronto. V. Dimitriadou received fee for service as a consultant. V. Dimitriadou and M. Minden designed and oversaw the conduct of the study.