Can an amino acid-based oral rehydration solution be effective in managing immune therapy-induced diarrhea?

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ABSTRACT

Immune checkpoint inhibitor (ICPi) therapy has transformed the way we treat cancer. However, its immune related adverse events (irAEs) can be debilitating and life threatening. Immune therapy-induced diarrhea (ITID) is one of the most commonly encountered irAEs and can lead to expensive and prolonged hospitalizations. The current standard of care for grade 3 or 4 ITID involves ICPi discontinuation, the initiation of steroids, and infliximab for refractory disease. This treatment regimen reverses the desired anti-tumor effect of ICPis, can lead to side effects, and is cost-ineffective. We report the first case of the successful treatment of grade 3 ITID with steroids and an amino acid-based oral rehydration solution (AA-ORS), enterade. Research suggests that AA-ORS may be used to reduce diarrhea and adequately hydrate patients, in contrast to glucose-based oral rehydration solutions, which have been implicated as a contributing factor to diarrhea in cancer patients. We hypothesize that an AA-ORS may mitigate ITID via safer and more economically viable means than the current standard of care, but more controlled trials are needed to test this hypothesis.

Introduction

Immune checkpoint inhibitors (ICPis), which led to the 2018 Nobel Prize in Physiology or Medicine [1], are monoclonal antibodies that inhibit immunosuppressive checkpoint protein-ligand interactions used by evasive tumor cells. These drugs target the programmed cell death-1 receptor (PD-1), its ligand (PD-1L), or the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) [2], as shown in Fig. 1. The relatively recent successes of these agents against various malignancies have established their routine use in patients with advanced disease [3–6]. As the use of ICPis increases, managing their immune related adverse events (irAEs) that affect the skin, lungs, liver, colon, and endocrine organs, though more rarely affecting the nervous, rheumatologic, and renal systems is important with regards to minimizing dosing interruption and/or attenuation [7,8]. While various studies have shown that combination therapy with a PD-1 inhibitor and CTLA-4 inhibitor e.g., nivolumab/ipilimumab has greater efficacy than monotherapy, it comes at the expense of increased risk to irAEs [9,10]. Gastrointestinal (GI) toxicity is among the most common irAEs [11] and can be debilitating if grade 3 or above (Table 1) [7,12,13]. It can range from mild, self-limiting diarrhea to ICPi-induced colitis necessitating hospitalization [14]. A phase III trial of combination nivolumab/ipilimumab for melanoma found GI toxicity in 15% of patients [15], while a recent 2018 systematic review of patients taking combination nivolumab/ipilimumab for melanoma showed the incidence of colitis to be 9–18% and diarrhea to be 34–45% [16].

Since irAEs are driven by non-specific T-cell activation and infiltration, treatment focuses on immunosuppression [14]. According to the 2018 American Society of Clinical Oncology clinical practice guidelines, the standard of care for grade 3 colitis is permanent CTLA-4 agent discontinuation and temporary cessation of PD-1 and PD-1L agents until patients recover to at least grade 1. For grade 4 colitis all ICPi treatment should be permanently discontinued. For both grade 3 and 4 colitis patients should be hospitalized for dehydration or electrolyte abnormalities and immediately receive corticosteroids. GI consult with appropriate workup (endoscopy, blood/stool testing, inflammatory markers, imaging) should be considered. Second line therapy with infliximab is recommended at 5–10 mg/kg within 2–3 days of symptoms refractory to corticosteroids [17]. However, therapy recommendations are unclear if symptoms persist despite treatment with infliximab [18]. There are multiple underlying drawbacks to this treatment approach. First, discontinuation of ICPis and subsequent immunosuppressant initiation reverses the desired immunostimulatory anti-tumor effect and could allow malignancy progression. Second, corticosteroids and infliximab carry side effects. Corticosteroids are known to cause insomnia, hyperglycemia, mood disturbances,
100 mg vial would cost nearly $10,000. Future research must
corresponding to REDBOOK Online, the wholesale acquisition cost of one
relatively inexpensive, the cost of in
ache, and increased risk of infection. Third, although corticosteroids are
relatively inexpensive, the cost of in
the cost of infliximab is quite substantial. Accor-
ding to REDBOOK Online, the wholesale acquisition cost of one
100 mg vial of infliximab is $1167.82 [19]. Given that 50% of patients
with steroid-refractory colitis required multiple doses of infliximab
[20], this therapy can be expensive. Therapy for an average 80 kg pa-
tient requiring two doses of infliximab at 10 mg/kg and $1167.82/
100 mg vial would cost nearly $10,000. Future research must find
avenues to not only mitigate irAEs, but to also do so through safer and
more economically viable means.

Case report

Our patient was a 62-year-old female who originally presented to
the University of Kentucky with neurologic deficits. Imaging revealed
several brain masses, which prompted two craniotomies with parietal
and temporal mass resections. Pathology confirmed malignant mela-
noma, but staging scans and dermatologic evaluation did not reveal
disease elsewhere. Further genetic testing revealed the tumor was BRAF
negative. Residual brain metastases were treated with gamma knife
surgery. Medical oncology began adjuvant combination nivolumab/
ipilimumab and our patient underwent two cycles of immunotherapy at
a cancer facility closer to home. Following her second cycle, she de-
veloped moderate diarrhea and was started on a prednisone taper be-
ginning at 60 mg daily. When her taper reached 15 mg daily, she pre-
vented to an outside hospital with worsening watery diarrhea, weight
loss, extreme fatigue, and poor appetite. Loperamide and diphenox-
ylate/atropine were ineffective, but stool studies were negative and she
was discharged. Nine days later she presented to the University of
Kentucky Emergency Department with the same complaints. Since her
discharge, she had consumed solely water and an over the counter
(OTC) sports drink as her symptoms were exacerbated with food. Other
symptoms included fever with chills and abdominal cramping. It had
been roughly three weeks since her immunotherapy.

The patient was hemodynamically stable and physical exam was
remarkable for an uncomfortable female with active bowel sounds and
diffuse abdominal tenderness with a Karnofsky performance score of
60%. Stool studies were negative (Clostridium Difficile by PCR,
comprehensive GI Panel by PCR, and Ova and Parasites). CT abdomen/
pelvis revealed large and distal small bowel mural hyper-enhancement
with fat stranding suggestive of chemotherapy related colitis/enteritis.
The working diagnosis was grade 3 ICPi-induced colitis based on her
severe abdominal pain and diarrhea necessitating hospitalization. No
other irAEs had been found or reported.

Methylprednisolone 2 mg/kg IV daily was initiated on hospital day
1 (Fig. 2). Loperamide was continued initially, and her diarrhea (Type 7
Bristol Stool Scale) began to improve. Due to persistent diarrhea despite
loperamide and diphenoxylate/atropine, anti-diarrheal agents were
discontinued on day 4 to better assess the patient’s stool burden, which
worsened the patient’s diarrhea. On hospital day 5 she experienced
increased stools associated with abdominal pain, food restriction, and
continued marked fatigue. On hospital day 6 the patient was started on
enterade, an amino acid-based oral rehydration solution (AA-ORS),
twice daily. Within 24 h her stools were of greater consistency (Type 6
Bristol Stool Scale) and decreased in frequency. After 72 h on enterade
her stools were formed (Type 5 Bristol Stool Scale) at two bowel
movements per day. Her abdominal pain and bloating resolved, her
appetite increased, and she became ambulatory. On hospital day 9 she
was discharged on prednisone and one 8 oz. bottle of enterade twice
daily.

Discussion

Chemotherapy and radiation injury to the gastrointestinal mucosa
occurs at the functional and structural levels. The damage often causes
reduced electrolyte and nutrient absorption, increased paracellular
permeability, translocation of bacterial products, mucositis, diarrhea,
and dehydration [21,22]. Glucose-based oral rehydration solutions (G-
ORS) were designed based on the sodium-coupled glucose transporter-1
(SGLT1) as it was well established that sodium and water absorption
were stimulated by glucose. However, despite correcting dehydration
and metabolic acidosis, G-ORS was shown to have minimal clinical
benefit in reversing acute diarrhea [23]. In fact, it was postulated that
in those with GI mucosal damage, the osmotic activity of unabsorbed
glucose in the lumen actually worsened diarrhea [24]. Based on further
research the World Health Organization released updated guidelines in
2006, advocating for the use of reduced osmolarity oral rehydration
solutions that decrease stool output by avoiding glucose-induced hy-
pertonicity [25]. More recent research has shown that glucose also
induces calcium-activated chloride secretion into the gastrointestinal
lumen, which coupled with glucose malabsorption secondary to cancer
therapy-induced villous atrophy, explains why G-ORS has had modest
success at best [23]. Considering that our patient’s only oral intake
prior to admission was water and an OTC sports drink (G-ORS), it
warrants consideration that the aforementioned mechanism played a
role in her ongoing diarrhea in addition to immune-related GI toxicity.

Along with glucose, amino acids are known to stimulate sodium and
water absorption [26,27]. A recent study showed that a mixture of lys-
ine, aspartic acid, glycine, isoleucine, threonine, tyrosine, valine,
tryptophan, and serine increased electrolyte absorption while de-
creasing paracellular permeability and plasma endotoxins in patients
with radiation-induced GI toxicity [28]. This added support to the
concept that an AA-ORS could reduce diarrhea in patients undergoing
cancer treatment.

Recent studies comparing AA-ORS and G-ORS have shown varied
results. One group demonstrated that an AA-ORS led to greater fluid
retention and interstitial volume restoration for hypertonic dehydra-
tion, in addition to superior electrolyte replacement and interstitial
fluid volume preservation during isotonic dehydration compared to a G-
ORS [29]. In contrast, another group’s randomized clinical trial
(NCT03262597) showed G-ORS to be slightly superior, although compa-
rable to AA-ORS in optimizing hydration using the beverage hydra-
tion index [30]. It must be stated that neither study examined these
effects in patients undergoing cancer treatment. Therefore, it remains

Fig. 1. Key immune checkpoint regulators involved in anti-tumor effects.
unclear whether AA-ORS or G-ORS shows superior efficacy in optimizing hydration status in cancer patients. We believe AA-ORS should be explored in cancer patients afflicted with diarrhea or dehydration secondary to cancer-related GI toxicity.

Enterade is a first-in-class, glucose-free amino acid-based oral rehydration solution with added electrolytes and natural sweetener. Enterade was developed by Dr. Vidyasagar at the University of Florida. Based on his preclinical in vivo data on irradiated mouse models, Dr. Vidyasagar demonstrated that enterade was able to treat dehydration and hence improve survival as compared to mice treated with normal saline and a random mixture of amino acid-based ORS [28]. This was later determined to be the result of gut regeneration, and further in vivo data confirmed that enterade increases crypt count and villus length, as well as sodium and chloride absorption [31]. Nutrition information can be found in Fig. 3. Since enterade is classified as a medical food, it is available without a prescription for about $5 per 8 oz. bottle. The recommended dose is two bottles per day, which must be taken 30 min before meals or one hour after. At present, there is only one active phase II trial studying its use in the treatment of diarrhea in neuroendocrine tumor patients (NCT03722511). Two other trials designed to study the use of enterade in patients with inflammatory bowel disease (NCT03451253) or short bowel syndrome (NCT03105362), respectively, are mentioned on clinicaltrials.gov, but their current status is unknown. A pilot study researching the anti-diarrheal efficacy of enterade in neuroendocrine tumor patients showed that 73.9% of patients reported improvement in diarrhea and 52.2% of patients reported a > 50% reduction in diarrhea frequency [32]. This prompted the design and registration of the aforementioned phase II clinical trial in neuroendocrine tumor patients, which is now open to accrual (NCT03722511).

### Conclusion

Based on this anecdotal case report of a patient with grade 3 ICPI-induced colitis showing drastic improvement upon enterade initiation, we hypothesize that this AA-ORS may have benefit in patients being treated for immune therapy-induced diarrhea (ITID). Further controlled studies are needed to determine whether AA-ORS is effective in managing ITID. Developing supportive care agents that are non-toxic and inexpensive has the potential of significantly impacting outcomes given the risk of permanently discontinuing or interrupting effective ICPI therapy. The prompt treatment of grade \( \geq 3 \) GI-irAEs via AA-ORS with or without corticosteroids would allow patients to resume their immunotherapeutic plan following symptom resolution, which is relevant for patients with limited treatment options. Also, the avoidance of prolonged corticosteroids and immunosuppressive therapy reduces the risk of side effects and opportunistic infections, while additionally allowing the continuation of the intended ICPI-induced anti-tumor effect. In addition, AA-ORS could significantly reduce patient and hospital costs. Even if combined with corticosteroids, solely forgoing infliximab could reduce overall expenses nearly 1000-fold. In conclusion, this report on the use of the AA-ORS, enterade, resulting in a positive outcome in a patient with grade 3 ICPI-induced colitis, coupled with the aforementioned potential benefits of AA-ORS suggest that this is a viable and cost-effective treatment option. Further ITID research is needed to improve the current treatment guidelines.
The design of the immune checkpoint inhibitor illustration (Fig. 1).

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Appendix A. Supplementary data

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Fig. 3. Enterade nutrition facts.

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Conflicts of interest

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References


