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Managing TKI-induced gastrointestinal toxicity in renal cell carcinoma (RCC)



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This series of videos is designed to support education within the uro-oncology community, raising awareness of pertinent topics related to the management and optimisation of therapy for renal cell carcinoma (RCC). It aims to enhance patient care standards and assist healthcare providers in optimising patient outcomes when treating RCC, offering valuable guidance on managing situations where clear directives may be lacking, and only expert recommendations are available.

TKIs in kidney cancer and introduction to gastro toxicities

This discussion, led by Dr Ricky Frazer, delves into the management of TKI-induced gastrointestinal toxicity, particularly diarrhoea, in renal cell carcinoma patients. Since their introduction in 2006, TKIs have played an important role in renal cancer, but potential associated adverse effects can significantly impact patients' quality of life. Diarrhoea remains one of the most common and challenging toxicities to manage, prompting the need for careful differentiation between causes, particularly in cases where checkpoint inhibitors are also involved.

Gastroenterologist Dr Sreedhar Subramanian joins Dr Frazer to explore the investigation and management of TKI-related diarrhoea. Dr Frazer presents a case of a patient treated with an IO/TKI combination following nephrectomy and metastases, seeking expert guidance on baseline tests, stool analysis, blood work, and risk factor identification.

Baseline testing and risk factors for diarrhoea

Dr Subramanian acknowledges the evolving nature of this field, noting that even gastroenterologists are still refining their approach to managing these toxicities effectively. He highlights the importance of establishing baseline stool frequency and considering a patient's surgical history—such as prior cholecystectomy or bowel resections—as these factors can influence bowel habits. While routine stool testing is not always necessary, understanding a patient's normal bowel patterns can be invaluable in assessing changes.

Dr Frazer further discusses a patient who developed diarrhoea after initiating combination therapy, which worsened post-meals but did not present with blood or urgency. Initially assuming a TKI-related cause, the patient was treated with loperamide, leading to the question of when a gastroenterologist should be consulted.

What symptoms should prompt an oncologist to reach out to a gastroenterologist?

Dr Subramanian agrees with the initial approach but stresses key warning signs requiring specialist input, such as bloody stools or nocturnal diarrhoea, which could indicate inflammatory colitis linked to checkpoint inhibitors. He also underscores the need to check for infections like C. difficile and consider alternative causes, such as pancreatic insufficiency, especially in patients with previous gastrointestinal surgeries.

The discussion references research which found that many patients referred for severe diarrhoea had underlying secondary causes, including bile salt diarrhoea, pancreatic insufficiency (particularly in diabetics), and small bowel bacterial overgrowth (SIBO). Dr Subramanian highlights the need to consider these factors in persistent cases.

What investigations and why?

When discussing investigations oncologists can initiate before referring to a gastroenterologist, he recommends non-invasive baseline tests such as stool culture, C. difficile testing, faecal calprotectin (to assess inflammatory diarrhoea), and faecal elastase (to evaluate pancreatic function). These tests help distinguish between immune-related and non-inflammatory diarrhoea, guiding further management before specialist consultation.

Interpreting test results is another critical aspect of diarrhoea management.

Dr Subramanian explains that low magnesium is a frequent finding in patients with diarrhoea and that faecal elastase, which measures pancreatic function, may yield borderline results if stools are too loose, necessitating retesting. A normal calprotectin level suggests non-inflammatory diarrhoea, whereas a SeHCAT scan can diagnose bile salt malabsorption (BAM), a condition that leads to postprandial diarrhoea and can be managed with bile salt binders. However, access to this scan is often limited. Additional considerations include pancreatic insufficiency, frequently associated with chronic pancreatitis or surgical history, which can be diagnosed via faecal elastase and treated with enzyme replacement therapy. SIBO, resulting from bacterial colonisation of the small intestine, is another cause of diarrhoea that can be diagnosed using a hydrogen breath test, though this method can be unreliable, especially in patients with prior intestinal surgeries.

Diarrhoea management

For BAM management, bile salt binders such as cholestyramine (a powder with poor palatability) or colesevelam (a more tolerable tablet form) are recommended. Proper timing of administration is crucial—bile salt binders should be taken at least 30 minutes before meals, with an hour-long gap before taking other medications to prevent interactions (e.g., contraceptive failure). General diarrhoea management begins with ruling out inflammatory causes and infections, followed by symptomatic treatment with loperamide (2 mg after each loose stool) to help control symptoms. Dietary adjustments, such as reducing lactose intake or following a FODMAP diet under dietitian supervision, can also be beneficial. Oncologists should review a patient's cancer treatment regimen to identify possible contributors to diarrhoea.

Differences between IO-induced and TKI-induced diarrhoea

Differentiating TKI-induced from immunotherapy-related diarrhoea involves key indicators: Blood in stools or nocturnal diarrhoea suggests inflammatory colitis, while faecal calprotectin testing helps distinguish inflammatory from non-inflammatory diarrhoea, though false positives are possible. Checkpoint inhibitor-induced colitis can mimic other conditions, requiring careful assessment. Clinicians can refer to BSG guidelines on immunotherapy-induced colitis, oncology society recommendations, and global gastroenterology guidelines on TKI-related diarrhoea. Collaboration with local gastroenterologists is crucial for managing complex cases.

Summary

Dr Frazer concludes the discussion by revisiting the patient case he had previously mentioned revealing that the patient's diarrhoea was ultimately due to bile acid malabsorption and was successfully managed with appropriate treatment. The key takeaway is that not all diarrhoea should be assumed to be TKI-related—consideration of other treatable causes is essential. Effective diarrhoea management ensures that patients can continue oncology treatments without unnecessary interruptions, ultimately improving their overall quality of life.

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