Digestive toxicity

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Immune-mediated side effects that affect the digestive system are mainly gastrointestinal (colitis being the most common and potentially the most serious) and hepatic in nature.

GASTROINTESTINAL TOXICITY

The incidence of diarrhoea among patients treated with anti-CTLA4 is 27-54%, while the incidence of colitis ranges from 8-22%. Bowel perforation is reported in 1% of cases (ipilimumab).

Liquid diarrhoea is the principal symptom and it may be accompanied by abdominal pain, haematochezia and fever (which are indicators of greater severity). Diarrhoea and/or colitis may occur months after the end of treatment with immunotherapy and may mimic inflammatory bowel disease.

The clinical condition can be categorised as grade 1 (<4 liquid stools/day, good general condition), grade 2 (4-6 liquid stools/day, or abdominal pain or haematochezia or nausea or nocturnal episodes, without affecting the patient's general condition), grade 3 (>7 liquid stools/day, incontinence, affecting the patient's general condition, requires hospitalisation) or grade 4 (life-threatening severity, urgent intervention indicated), depending on the severity.

There are no prophylactic treatments for immune-mediated colitis.

From grade 2 and above, it is advisable to perform a complete blood panel (blood count, clinical chemistry, TSH, CRP and ESR), as well as a stool analysis (stool culture, Clostridium toxin, parasites, etc.). On the other hand, in more serious cases, it is recommended to perform the screening prior to the administration of an anti-TNF (viral serologies, HIV, QuantiFERON, etc.). The role of faecal calprotectin in this patient profile is not well established, although it would seem that it may help to suspect an inflammatory cause and during follow-up.

Proctosigmoidoscopy/colonoscopy is recommended for persistent grade 2 toxicity and for grade 3/4. The findings may range from a normal colonic mucosa to exudates, granularity, loss of vascular pattern and ulcerations.

Regarding treatment, in grade 1, symptomatic treatment, astringent (anti-diarrhoea) diet, hydration and anti-diarrhoeal drugs are recommended. In grade 2, treatment with immunotherapy should be suspended and oral corticosteroids started, while in grades 3-4, treatment with IV corticosteroids (1-2 mg/kg/day) is recommended, and if there is

no response on the 3rd day, treatment with infliximab should be started. Cases have been reported that have responded to treatment with vedolizumab.

HEPATOTOXICITY

The incidence of hepatitis as an adverse effect of immunotherapy is 5-10% (1-2% of which is grade 3) in patients treated with ipilimumab, nivolumab and pembrolizumab in monotherapy, while this rises to 25-30% in those patients treated with two drugs in combination (ipilimumab and nivolumab).

It is recommended that all patients who are going to receive treatment with immunotherapy should undergo baseline lab tests with liver function tests (transaminases, bilirubin, albumin, etc.) and viral serology testing (HBV, HCV and HIV), repeating the determination of transaminases and bilirubin prior to each cycle.

In most cases when hepatitis is diagnosed, the patient is asymptomatic and the elevation of transaminases is detected in the routine check-up (but jaundice, fatigue, etc. may also be detected). A differential diagnosis is very important in the event of elevated transaminase levels. A thorough anamnesis should be performed to ascertain the existence of concomitant symptoms (fever, abdominal pain, jaundice, pruritus, etc.), all the drugs that the patient has received, if he/she has taken herbal products, if he/she consumes alcohol or other drugs, etc.

Depending on the transaminase levels, hepatitis will be classified as grade 1 (ALT or AST>ULN-3xULN), grade 2 (ALT or AST 3-5x ULN), grade 3 (ALT or AST 5-20x ULN) or grade 4 (ALT or AST> 20x ULN).

For grade 1 hepatitis, treatment with immunotherapy can be continued and the lab tests can be repeated after one week.

In grade 2 hepatitis, it is advisable to delay treatment and repeat the lab tests with liver function tests every 3 days, as well as to repeat viral serologies (HAV, HBV, HCV, HEV), autoimmune hepatitis autoantibodies, ferritin, TSH, and to assess a liver imaging test (ruling out metastasis, vascular thrombosis, etc.). If the results are negative and elevated transaminase levels persist, or there is grade 3/4 of toxicity, it is advisable to start treatment with corticosteroids (1-2mg/kg/day). If, after three days of treatment with intravenous corticosteroids there is no improvement, it is recommended to start mycophenolate.

A liver biopsy should be considered in cases of severe hepatitis, for differential diagnosis (the most common finding is lobular hepatitis indistinguishable from autoimmune hepatitis).