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Original Research

Evolution and recurrence of gastrointestinal immune-related adverse events induced by immune checkpoint inhibitors

Alice de Malet [a], Guillemette Antoni [b], Michael Collins [a,c], Emilie Soularue [a,c], Lysiane Marthey [a], Thibaut Vaysse [a], Clelia Coutzac [d], Nathalie Chaput [d,e], Christine Mateus [f], Caroline Robert [f], Franck Carbonnel [a,c,*]

[a] *Department of Gastroenterology, Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), 94270, Le Kremlin-Bicêtre, France*
[b] *INSERM SC10-US19, Villejuif, France*
[c] *University Paris-Saclay, Faculté de Médecine, Le Kremlin-Bicêtre, 94276, France*
[d] *Laboratory of Immunomonitoring in Oncology, CNRS-UMS 3655 and INSERM-US23, Gustave Roussy Cancer Campus, 114 Rue Edouard Vaillant, Villejuif, F-94805, France*
[e] *University Paris-Saclay, Faculté de Pharmacie, Chatenay-Malabry, F-92296, France*
[f] *Département of Medecine, Dermatology Unit, Gustave Roussy Cancer Campus, 114 Rue Edouard Vaillant, Villejuif, F-94805, France*

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Abstract ***Background:*** Immune checkpoint inhibitors (ICIs), such as anti–CTLA-4 and anti–PD-1 antibodies, are effective against several malignancies. They are associated with gastrointestinal immune-related adverse events (GI-IrAEs), which may be severe and lead to ICI discontinuation. We assessed the risk of evolution of GI-IrAEs to chronic GI inflammation and the risk of recurrence after a second line of ICI.
Patients and methods: This was a single-centre study. Included patients had a GI-IrAE due to ICIs between September 2010 and July 2017. We assessed the persistence of symptoms, endoscopic and/or histological inflammation, and the risk of recurrent GI-IrAEs after the second line of ICIs.
Results: Eighty patients were included. The median follow-up was 8.4 months (0.36–72.3). The median duration of GI symptoms was 1.5 months (5 days–10.3 months): 1.4 months (7 days–4.9 months) with anti–CTLA-4, 2.0 months (5 days–10.3 months) with anti–PD-1 and 1.0 month (8 days–3.4 months) with combination therapy (log-rank test: $p = 0.02$). Three and 6 months after

* *Corresponding author*: Hôpital Bicêtre, Service de Gastroentérologie, 78 Rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France. Tel.: +33145213722.
E-mail address: franck.carbonnel@aphp.fr (F. Carbonnel).

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the beginning of GI-IrAEs, 22% (95% confidence interval: 14%–33%) and 5.4% (2.0%–14.7%) of patients had persistent symptoms, respectively. After a median of 6 months, 20/27 patients had endoscopic and/or histological inflammation, of whom, seven were symptom free. After the first episode, 6/26 patients relapsed after receiving another course of ICIs. Among these 26, 89% (77%–100%) had no recurrence after 3 months, 71% or 95% if the second line was anti–CTLA-4 or anti–PD-1, respectively.

Conclusion: GI-IrAEs seem to be acute or subacute, not chronic. Reintroduction of ICIs is possible in patients who had GI-IrAE.

1. Introduction

Immunotherapy with immune checkpoint inhibitors (ICIs), such as anti–CTLA-4 antibodies (ipilimumab, and tremelimumab), anti–PD-1 (nivolumab, and pembrolizumab) and anti-PD(L)-1 (i.e. durvalumab, atezolizumab, avelumab), is an effective treatment option for metastatic melanoma and several other malignancies (non–small-cell lung cancer, renal cell cancer, Hodgkin's disease, urothelial carcinoma, head and neck carcinoma, gastric cancer, hepatocellular carcinoma, microsatellite instability tumours, sarcoma, and Merkel carcinoma) [1–15]. ICIs can be used as monotherapy, or as a combination of anti–CTLA-4 and anti-PD(L)-1 therapy, which is more effective but also more toxic [3,16,17]. ICIs cause immune-related adverse events (IrAEs), including enterocolitis, gastritis and microscopic colitis [18–24]. These gastrointestinal (GI)-IrAEs may be severe but generally respond well to corticosteroids and infliximab [20,25–28]. The long-term risk of progression to chronic inflammation of the GI tract is unknown. It is important to assess the risk/benefit ratio of ICIs because their indications are likely to expand to patients with cancer at earlier stages, whose life expectancy can reach decades [29]. Furthermore, discontinuation rates of ICIs range between 3 and 12% in anti–PD-1 trials and between 3 and 25% in anti–CTLA-4 trials. GI-IrAEs are one of the leading causes of discontinuation of ICIs [27]. The question of reintroduction of ICIs after GI-IrAEs is of fundamental importance in informing treatment decisions.

The aims of this study were the following: (1) to determine the risk of chronic GI inflammation in patients who experience a GI-IrAE with anti–CTLA-4, and/or anti–PD-1 or anti–PD(L)-1, and (2) to determine the risk of recurrence of GI-IrAE after a second-line treatment with ICIs.

2. Patients and methods

2.1. Patients

This was a single-centre study. All consecutive patients who had experienced a GI-IrAE (enterocolitis and/or gastritis) with anti–CTLA-4, anti–PD-1/anti–PD(L)-1 or both, between September 2010 and June 2017 were prospectively recorded. GI-IrAEs were defined as clinical symptoms associated with endoscopic and/or histological inflammation, either located in the upper GI tract (oesophagus, stomach and/or duodenum) or lower GI tract (ileum and/or colon). Patients who had a documented intestinal infection or who lacked adequate clinical data were not included.

2.2. Collected data

The following baseline data were collected from a retrospective analysis of chart reviews: patients' characteristics (personal and family history of autoimmune or inflammatory diseases, including inflammatory bowel disease, cancer site and histology); history of treatment with ICIs and characteristics of GI-IrAEs (the date of diagnosis, site of inflammation, grade of severity, therapy and associated non–GI-IrAE). GI-IrAEs were categorised in several entities, as previously reported: acute enterocolitis, microscopic colitis and upper GI inflammation [24]. We also investigated the duration of GI-IrAEs, recurrence and time from initiation of therapy to occurrence of GI-IrAE and further GI endoscopies and biopsies. Among patients who received a second ICI, we assessed the recurrence rate of GI-IrAEs, characteristics, severity, duration and therapy.

2.3. End-points

The main end-points were the following:

1) Duration of the initial GI-IrAEs (i.e., the first ICI course associated with GI-IrAEs), defined by persistent symptoms (diarrhoea, rectal bleeding, abdominal pain and vomiting). The date of the end of the initial GI-IrAEs was defined by the date of the first symptom-free visit when it was not followed by clinical relapse. In patients who relapsed, for instance during corticosteroid tapering, the date of the end of the initial GI-IrAEs was defined by the first symptom-free visit following the last relapse.
2) Persistence of endoscopic and/or histological signs of inflammation.
3) Risk of GI-IrAE recurrence with a second ICI.

2.4. Statistical analysis

Quantitative numerical variables are presented as median (range); qualitative variables are presented as the number and percentage. Quantitative variables were compared using the Student t-test and qualitative variables with the chi-squared test. The duration of GI-IrAEs was determined by the Kaplan–Meier method; patients who died, were lost to follow-up or received a second ICI before clinical cure were censored. The GI-IrAE recurrence-free survival after a second ICI was estimated by the Kaplan–Meier method. Patients who died, were lost to follow-up or received a third ICI before they relapsed were censored at the date of death, loss to follow-up or date of the third ICI prescription, respectively.

2.5. Ethics

This was a retrospective, observational study. According to the French law at the time of conception of the study, patients received written information about the fact that their medical charts could be studied for a research purpose. None of them refused. Database was completely anonymous.

3. Results

3.1. Patients' characteristics

A total of 118 patients were included for suspected GI-IrAEs. Thirty-eight patients were excluded for various reasons (Fig. 1). Therefore, a total of 80 patients were studied; their clinical characteristics are shown in Table 1. Most patients had either melanoma (60/80 = 75%) or non–small-cell lung cancer (9/80 = 11%). Seventeen patients (21%) had a history of immune-mediated disease, including one with ulcerative colitis. Sixteen of 80 patients (20%) had already received another ICI, without GI toxicity, before the one associated with the GI-IrAE (four ipilimumab, three nivolumab, nine pembrolizumab). All patients werereferred to the Gastroenterology Department of Bicêtre Hospital (Paris, France) for GI-IrAEs. A majority of them (71/80) had received ICIs at Gustave Roussy Cancer Campus (Villejuif, France).

Patients with GI-IrAEs were treated according to a predefined protocol [23,25]. Briefly, patients with grade I or II GI-IrAEs were first treated with antidiarrhoeal drugs. Those who did not improve received budesonide or oral steroids at a dose of 1 mg/kg of the body weight. Patients with grade III or IV GI-IrAEs were prescribed intravenous corticosteroids at a dose of 1 mg/kg. Those who responded were switched to oral corticosteroids and tapered according to a fixed regimen, for a total duration of 3 months. Patients who failed to respond to intravenous steroids received infliximab at a dose of 5 mg/kg. Most patients received a single infusion of infliximab; some needed two infusions of infliximab. One patient received adalimumab for a severe proctitis after colectomy for IrAEs and immunisation towards infliximab. Another patient received vedolizumab after he had failed to respond to intravenous corticosteroids and infliximab (Supplemental Table 3).

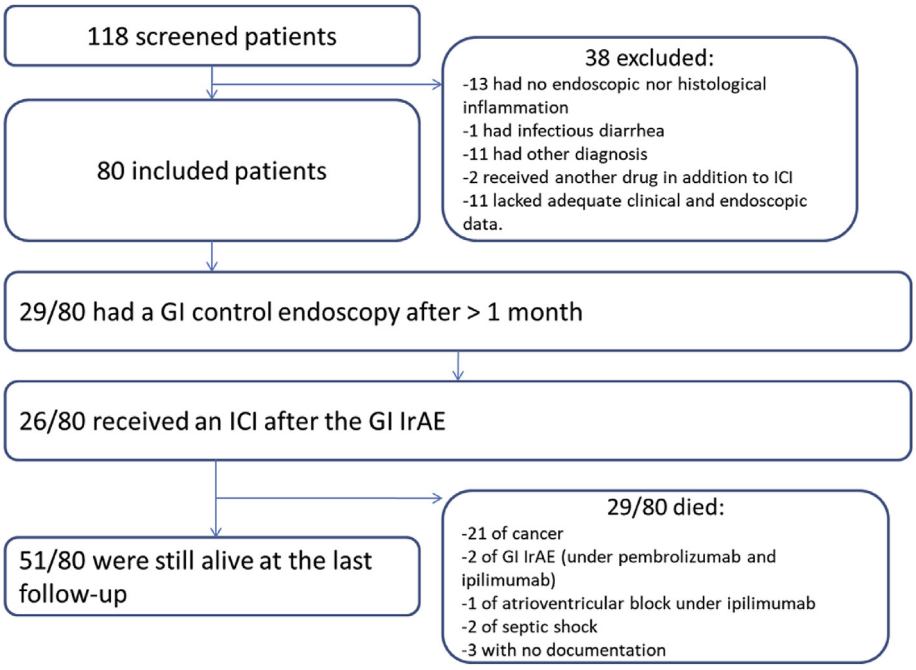

Fig. 1. Flowchart of the study population. ICI, immune checkpoint inhibitor; GI, gastrointestinal; IrAE, immune-related adverse event.

Table 1
Initial characteristics of the study population.

Characteristic	Total
Women: n (%)	39 (49%)
Age (years) at the time of GI-IrAE	61 [27–86]
History of inflammatory disease	
Ulcerative colitis	n = 1 (1%)
Ankylosing spondylitis	n = 1 (1%)
Raynaud's syndrome	n = 1 (1%)
Rheumatoid arthritis	n = 2 (3%)
Rheumatic fever	n = 1 (1%)
Psoriasis	n = 2 (3%)
Pyoderma gangrenosum	n = 1 (1%)
Vitiligo	n = 1 (1%)
Asthma	n = 3 (4%)
Sarcoidosis	n = 2 (3%)
Graves' disease	n = 1 (1%)
Hypothyroidism	n = 1 (1%)
History of allergy	
Drug allergy	n = 11 (14%)
Food allergy	n = 1 (1%)
Environmental pathogen allergy	n = 4 (5%)
Undefined	n = 3 (4%)
Cancer site	
Melanoma	n = 60 (75%)
Non–small-cell lung cancer	n = 9 (11%)
Prostate carcinoma	n = 2 (3%)
Renal carcinoma	n = 3 (4%)
Cervical carcinoma	n = 2 (3%)
Colorectal carcinoma (with microsatellite instability)	n = 1 (1%)
Ovarian carcinoma	n = 1 (1%)
Lymphoma	n = 2 (3%)
Cancer treatment before the immune checkpoint inhibitor that caused GI-IrAE	
Chemotherapy	n = 58 (73%)
Immune checkpoint inhibitor	n = 16 (20%)
Radiotherapy	n = 36 (45%)
Surgery	n = 63 (79%)

GI-IrAE, gastrointestinal immune-related adverse event.

3.2. Characteristics of the initial GI-IrAEs

Forty-five patients had a GI-IrAE due to anti–CTLA-4 (43 ipilimumab, 2 tremelimumab), 27 due to anti–PD-1 (11 nivolumab, 16 pembrolizumab) and eight due to an anti-CTLA-4/anti–PD(L)-1 combination (seven nivolumab/ipilimumab, one tremelimumab/durvalumab) (Table 2).

The median time from the first ICI injection to the onset of the first symptoms was 1.3 months (0–23): it was 1.1 months (0–23.5) in anti–CTLA-4, 3.4 months (0.1–21.5) in anti–PD-1 and 0.9 months (0–2.1) in combination therapy.

Among 80 patients with GI-IrAEs, 77 had a lower GI endoscopy. Fifty-one patients had an upper GI endoscopy; three of them had no lower GI endoscopy because they had severe upper GI inflammation and no diarrhoea.

Among the 80 patients, three patterns of GI-IrAEs were observed: 70 patients (88%) had an acute enterocolitis (44 were due to anti–CTLA-4, 19 due to anti–PD-1 and 7 due to a combination therapy), 6 (7.5%) had a microscopic colitis (five due to anti–PD-1 and one due to a combination therapy) and 4 (5%) had an exclusive, upper GI tract inflammation (three due to pembrolizumab and one due to ipilimumab).

The median follow-up was 8.4 months (0.36–72.3). Fifty-one patients were still alive at the last follow-up. Twenty-nine patients died: 21 patients died of cancer, two died of GI-IrAEs (while being treated with pembrolizumab and ipilimumab, respectively), one died of an atrioventricular block while being treated with ipilimumab, two died of septic shock and, in three patients, the cause of death was not documented. Extraintestinal IrAEs are shown in Supplemental Table 1. Endoscopic and histological characteristics are shown in Supplemental Table 2. Treatment of initial GI-IrAE is shown in Supplemental Table 3. Five patients were colectomised; none of them received a second-line ICI therapy.

3.3. Duration of GI-IrAEs

3.3.1. Clinical course

The overall median duration of symptoms was 1.5 months (5 days–10.3 months). It was 1.4 months (7 days–4.9 months) for anti–CTLA-4; 2.0 months (5 days–10.3 months) for anti–PD-1 and 1.0 month (8 days–3.4 months) for combination therapy (log-rank test: $p = 0.0195$). Among the 71 patients who received corticosteroids, a relapse occurred during corticosteroid tapering in 15/71 (21%) patients. At 3 months, 22% of patients (95% confidence interval [CI]: 14%–33%) still had symptoms, namely 12% (5.1%–26%), 41% (26%–64%) and 12% (2.0%–78%) with anti–CTLA-4, anti–PD-1 and combination therapy, respectively. At 6 months, only 5.4% (2.0%–14.7%) of patients had symptoms (Fig. 2).

In the acute enterocolitis group, the median duration of symptoms was 1.4 months (0.2–8.6); it was 1.4 months (0.3–8.6) with anti–CTLA-4, 2.0 months (0.2–8.6) with anti–PD-1 and 0.8 months (0.3–2.0) with the combination therapy. In the microscopic colitis group, the median duration of symptoms was 3.5 months (1.4–10.5), and in the upper GI tract inflammation group, it was 1.8 months (0.2–4.5).

3.3.2. Further endoscopic and histological data

After a median duration of 6 months (2–31) after the first symptom of GI-IrAEs, 29/80 patients had a control GI endoscopy (two had an upper endoscopy, 16 had a lower endoscopy and 11 had upper and lower endoscopies). Among these, 16/29 had sustained symptoms and 13/29 were symptom free. Twenty of 29 (69%) patients had endoscopic and/or histological inflammation, including 7/20 (35%) who were symptom free at the time of endoscopy. (Supplemental Figure 1)

3.4. Recurrence of GI-IrAEs after resuming ICIs

After the initial episode, 26 patients received a second course of ICI. The median time between the end of

Table 2
Characteristics of patients who had gastrointestinal immune-related adverse events (GI-IrAEs) due to immune checkpoint inhibitors: anti CTLA-4, anti–PD-1 or combination of both.

Variables	Anti–CTLA-4 (43 ipilimumab, 2 tremelimumab)	Anti-PD(L)-1(11 nivolumab, 16 pembrolizumab)	Combination therapy (7 nivolumab/ipilimumab, 1 tremelimumab/durvalumab)	Total (n = 80)
Time between the first dose of ICIs and first symptoms of GI-IrAEs (months)	1.1 [0–23.5]	3.4 [0.1–21.5]	0.9 [0.0–2.1]	1.3 [0–23]
The number of ICI infusions between the first dose of ICIs and first symptoms of GI-IrAEs	3 [1–8]	10 [1–32]	3 [1–5]	3 [1–32]
Upper GI symptoms	16 (36)	6 (22)	5 (63)	26 (33)
Nausea/vomiting (%)	16 (36)	6 (22)	5 (63)	26 (33)
Dyspepsia (%)	1 (2)	1 (4)	0 (0)	2 (3)
Epigastric pain (%)	1 (2)	4 (15)	2 (25)	6 (8)
Lower GI symptoms	43 (96)	25 (93)	8 (100)	76 (95)
Diarrhoea (%)	42 (93)	24 (89)	8 (100)	75 (94)
Rectal bleeding (%)	22 (49)	6 (22)	2 (25)	30 (38)
Abdominal pain (%)	42 (93)	24 (89)	8 (100)	75 (94)
Abdominal mass (%)	0 (0)	0 (0)	0 (0)	0 (0)
Anal abcess (%)	1 (2)	0 (0)	0 (0)	1 (1)
Anal fissure (%)	1 (2)	0 (0)	0 (0)	1 (1)
Anal fistula (%)	1 (2)	0 (0)	0 (0)	1 (1)
Other symptoms				
Mouth ulcers (%)	1 (2)	0 (0)	0 (0)	1 (1)
Arthralgia (%)	4 (9)	3 (11)	0 (0)	8 (10)
Fever > 38 °C or < 36 °C (%)	22 (49)	4 (15)	3 (38)	28 (35)
Tachycardia> 90/min (%)	24 (53)	5 (19)	1 (13)	29 (36)
Complications (%)	16 (36)	8 (30)	1 (13)	25 (31)
Intra-abdominal abcess (%)	3 (7)	0 (0)	0 (0)	3 (4)
Stenosis (%)	1(2)	0 (0)	0 (0)	1 (1)
Colectasia (%)	2 (4)	0 (0)	1 (13)	3 (4)
Perforation (%)	3 (7)	0 (0)	0 (0)	3 (4)
Sepsis (%)	2 (4)	0 (0)	1 (13)	3 (4)
Haemorrhage (%)	2 (4)	0 (0)	0 (0)	2 (3)
Acute renal failure	4 (9)	5 (19)	0 (0)	9 (11)
Hypokalaemia (<3 mmol/L) (%)	4 (9)	4 (15)	0 (0)	8 (10)
Gastrointestinal severity[a]				
Grade I (%)	1 (2)	1 (4)	0 (0)	2 (3)
Grade II (%)	8 (18)	5 (19)	3 (38)	16 (20)
Grade III (%)	19 (42)	12 (44)	4 (50)	35 (44)
Grade IV (%)	16 (36)	8 (30)	1 (13)	25 (31)
Grade V (%)	1 (2)	1 (4)	0 (0)	2 (3)
Harvey-Bradshaw index [38]	10 [3–24]	8 [0–21]	8 [6–14]	10 [2–24]
Laboratory tests				
Haemoglobin (g/dL)	11 [5–15]	12 [8–17]	12 [11–13]	12 [5–17]
C-reactive protein (CRP) (mg/L)	111 [5–403]	48 [5–182]	130 [7–331]	91 [5–403]

ICI, immune checkpoint inhibitor.
[a] Gastrointestinal severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4, depending on patients' predominant symptom: vomiting or diarrhoea.

symptoms of GI-IrAEs and the first infusion of the second course of ICIs was 1.1 months (0.1–32.6). (Table 3)

Among 18 patients who had a grade I–II IrAE with the first-line ICI, 10/18 (56%) subsequently received a second line of ICIs versus 16/60 (27%) of the 60 patients who had a grade III–IV IrAEs with the first line (Supplemental Figure 2).

Eighty-nine percent of patients (95% CI: 77%–100%) had no recurrence after 3 months; 71% (95% CI: 45%–100%) and 95% (95% CI: 85%–100%) if the second line was an anti–CTLA-4 and anti–PD-1, respectively. After 1 year, 80% of patients (65%–98%) had no recurrence; 57% (95% CI: 30%–100%) and 88% (95% CI: 74%–100%) if the second line was an anti–CTLA-4 and an anti–PD-1, respectively. There was a numerically higher recurrence rate when the second line was an anti–CTLA-4 rather than an anti–PD-1 (log-rank test: 0.11) (Fig. 3). There was no significant difference in recurrence-free survival according to whether the second line was the same as the first or different (log-rank test: 0.53) (Fig. 4).

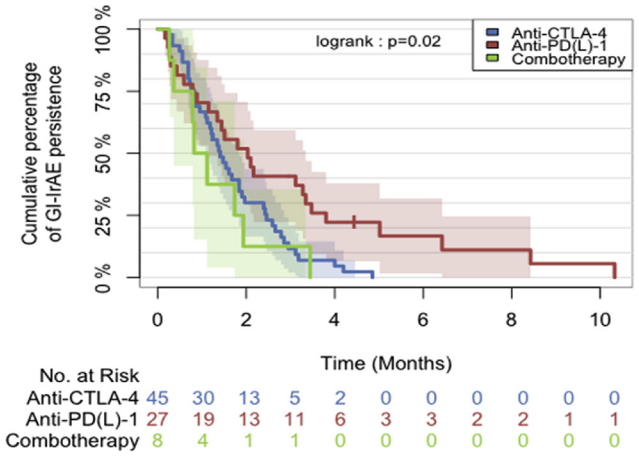

Fig. 2. Cumulative percentage of persistence of gastrointestinal immune-related symptoms after anti−CTLA-4, anti−PD-1 and combination therapy (log-rank test: $p = 0.02$). GI-IrAE, gastrointestinal immune-related adverse event.

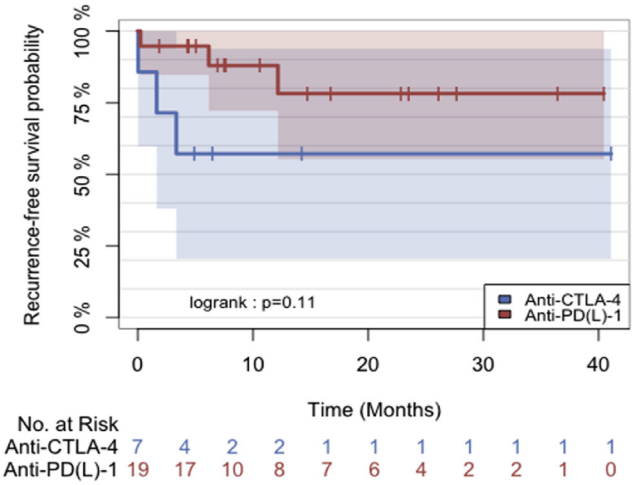

Fig. 3. Comparison of gastrointestinal immune-related adverse recurrence-free survival probability according to whether the second course was anti-CTLA-4 or anti-PD(L)-1 (log-rank test: $p = 0.11$).

Among the six patients who relapsed under the second ICI, the recurrence severity was grade I for 2/6 (33%), grade II for 2/6 (33%) and grade IV for 2/6 (33%); the outcome was favourable under medical treatment. No patient required colectomy. Nine patients had a control endoscopy before starting the second line: 7/9 (66%) had endoscopic and/or histological signs of activity and among these, 2/7 (33%) relapsed under the second ICI and two had no endoscopic and/or histological signs of activity and among these, none relapsed under the second ICI.

3.4.1. Extraintestinal IrAE occurrence after resuming ICIs

Among the 26 patients who received a second course of ICI, six had a non−GI-IrAE; none of them had an associated GI-IrAE recurrence. All IrAEs were either grade I or II. Five patients had a cutaneous IrAE (four grade I, one grade II), including one with an associated arthritis (grade I) and one with an associated arthritis (grade II) and a dry-eye syndrome (grade II). One patient had a grade II autoimmune hepatitis (Table 4).

4. Discussion

In this study, we assessed the evolution and recurrence risk of GI-IrAEs in patients who have received ICIs. This information is important for patients who suffer this type of complication. In contrast to the direct cytotoxic action of traditional antineoplastic agents, ICIs enhance anticancer T-cell activity. This leads to a systemic loss of tolerance, with resulting IrAEs, of which GI-IrAEs are among the most frequent and severe. Diarrhoea associated with chemotherapy is due to the direct toxicity of drugs or drug metabolites on the intestines. It usually stops rapidly after drug discontinuation. The mechanisms of GI-IrAEs are different and probably related to the imbalance between the activation of effector T-cell activation and depletion or

Table 3
Recurrence of gastrointestinal immune-related events (GI-IrAEs) in patients who received a second course of immunotherapy after a first GI-IrAE.

Drugs	First line	Second line	Recurrence of GI-IrAEs after second line	Grade of GI-IrAE toxicity	
				First line	Second line
Anti−CTLA-4	$N = 45$	Anti−CTLA-4: $n = 6$	2/6	2	1
				3	2
		Anti−PD-1: $n = 11$	2/11	4	1
				1	4
		Combination therapy: $n = 0$			
Anti−PD-1	$N = 27$	Anti−CTLA-4: $n = 1$	1/1	2	4
		Anti−PD(L)-1: $n = 5$	1/5	3	2
		Combination therapy: $n = 0$			
Combination therapy	$N = 8$	Anti−CTLA-4: $n = 0$			
		Anti−PD-1: $n = 3$	0/3		
		Combination therapy: $n = 0$			

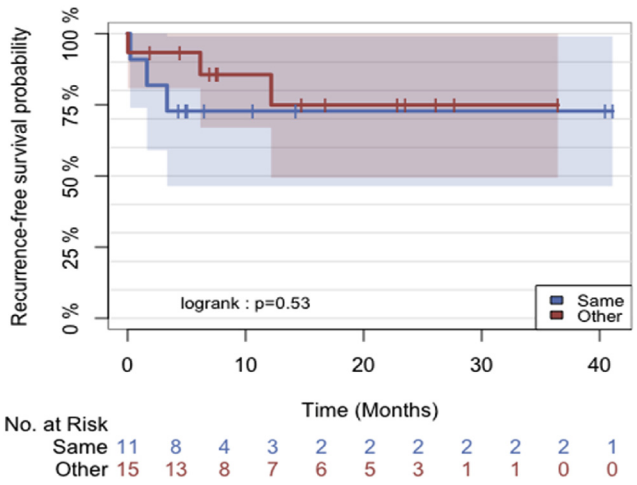

Fig. 4. Comparison of gastrointestinal immune-related adverse recurrence-free survival probability according to whether the second course was the same as the first or different (log-rank test: $p = 0.53$).

ineffectiveness of T_{reg} [30–34]. GI-IrAEs resemble inflammatory bowel disease as regards symptoms, endoscopy and treatment [23]. An increasing number of patients who receive ICIs have prolonged survival [29], and it is crucial to know whether there is a risk of chronic GI inflammation triggered by these drugs.

We found that the median duration of symptoms of GI-IrAEs was 1.5 months and was shorter in patients treated with anti–CTLA-4 than in those treated with anti–PD-1, particularly those with microscopic colitis. Furthermore, intestinal inflammation was found in 69% of patients who had lower GI endoscopy after a median duration of 6 months after the GI IrAEs; 35% of these patients were symptom free. In our study, these patients did not evolve to chronic GI inflammation. However, the case of a patient who developed an Inflammatory bowel disease (IBD) 2 years after grade III ipilimumab-induced enteritis and ipilimumab discontinuation was recently reported [35].

We found that 89% and 80% of patients who received a second line of ICI after GI-IrAEs were symptom free after 3 months and 1 year, respectively. There was a numerically, although non-statistically significant, higher risk of relapse of GI-IrAEs in patients who received anti–CTLA-4 compared with those who received anti–PD(L)-1. Very little data are available concerning the risk of recurrence of GI-IrAEs in patients who receive a second line of ICI. In this study, the three patients with GI-IrAEs associated with anti–PD-1/anti–CTLA-4 combination therapy tolerated subsequent anti–PD-1 monotherapy well. In a recent study, enterocolitis recurred in only 6% of patients on anti–PD-1 rechallenge after combination therapy discontinuation [36]. Another study assessed the risk of new and recurrent IrAEs in patients who had an IrAE under ipilimumab and subsequently received an anti–PD-1 [37]. Only one of a total of 47 patients (2%) with prior colitis with ipilimumab had a recurrence of colitis with anti–PD-1. From these data and ours, the risk of recurrent GI-IrAEs seems limited. However, in the study by Menzies *et al.* [37], 8 (40%) of 20 patients who had a non–GI-IrAE with ipilimumab had a new onset colitis with anti–PD-1.

Our study has limitations inherent to its retrospective design. Furthermore, patients who recommenced on ICIs had a less severe form of GI-IrAEs than the population of patients not treated with a second ICI. Consequently, our

Table 4
Occurrence of extra–GI-IrAEs in patients who received a second course of immunotherapy after a GI-IrAE.

>Drugs	First line	Second line	Occurrence of extra–GI-IrAE after 2nd second line and type	Grade of toxicity	
				First line: GI-IrAE	Second line: Extra–GI-IrAE
Anti–CTLA-4	$N = 45$	Anti–CTLA-4: $n = 6$	1/6: 1 articular + cutaneous	2	1
		Anti–PD-1: $n = 11$	2/11: 2 cutaneous	4 4	1 2
		Combination therapy: $n = 0$			
Anti–PD-1	$N = 27$	Anti–CTLA-4: $n = 1$	0/1		
		Anti–PD(L)-1: $n = 5$	1/5: 1 articular + cutaneous + dry eye	3	1
		Combination therapy: $n = 0$			
Combination therapy	$N = 8$	Anti–CTLA-4: $n = 0$			
		Anti–PD-1: $n = 3$	2/3: 1 cutaneous 1 hepatic	2 3	1 2
		Combination therapy: $n = 0$			

GI-IrAE, gastrointestinal immune-related event.

findings may be more applicable to a population of patients with less severe forms of GI-IrAEs.

This article has important practical consequences. Patients and physicians should be informed that the duration of GI-IrAEs is limited. This should reassure patients who endure these complications. In addition, our data support the current guidelines that do not recommend treating patients with GI-IrAEs with immunosuppressive maintenance therapy [25,26]. Yet, we show that intestinal inflammation may persist after resolution of GI symptoms. Patients with persisting intestinal inflammation should be followed-up in the long term. Further long-term studies should determine whether GI inflammation resolves or persists.

5. Conclusion

In summary, this study shows that GI-IrAEs are acute or subacute, not chronic. Reintroduction of ICIs is relatively safe in patients who had GI-IrAEs; it should be discussed on case-by-case basis, within a multidisciplinary team.

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Conflict of interest statement

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All remaining authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.006.

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