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Systematic or Meta-analysis Studies

Immune checkpoint Inhibitor–Induced diarrhea and Colitis: Incidence and Management. A systematic review and Meta-analysis

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have improved cancer outcomes. However, immune-related adverse effects are common. The aim was to investigate the incidence of diarrhea and colitis of ICIs alone and in combination with chemotherapy or tyrosine kinase inhibitors (TKIs), histopathological findings, and management.

Methods: Two separate studies, including meta-analyses, were performed. Key inclusion criteria were for Study I) phase I-IV trials, and data on diarrhea and/or colitis; for Study II) studies describing histopathologic and endoscopic findings and/or biologic treatment for ICI-induced colitis.

Results: The incidence of anti-PD-1/PD-L1 antibody-induced diarrhea and colitis was 10% and 2%, respectively, with no clinically relevant differences between the compounds. The CTLA-4 inhibitor, ipilimumab, induced diarrhea and colitis in 33% and 7% of patients, respectively, whereas the incidence of diarrhea and colitis following ipilimumab combined with nivolumab was 21%-37% and 4%-8%, depending on regimen. The incidence of all-grade diarrhea following ICIs combined with chemotherapy or TKIs was high (17%-56%), whereas only 0.5% of patients developed severe (≥ grade 3) colitis. The main patterns of histopathologic presentation after PD-1/CTLA-4 inhibitor mono- or combination therapy were acute and chronic active colitis and microscopic colitis-like. Infliximab and vedolizumab were equally effective against ICI-induced colitis.

Conclusion: Expanding treatment options include combinations of ICIs and chemotherapy/TKI with a high incidence of diarrhea and a low incidence of colitis; thus, a potential risk of overtreatment with corticosteroids exists. We suggest a more tailored approach, particularly for the management of low-grade diarrhea. Prospective clinical trials are needed to refine management.

Introduction

The introduction of immune checkpoint inhibitors (ICIs) for different types of cancer constitutes a major breakthrough in the improvement of disease outcomes [1]. However, ICIs can cause various immune-related adverse events (irAEs) [2]. Following the initiation of ICIs, lower gastrointestinal (GI) events ranging from mild diarrhea to severe colitis [3] are commonly reported after 6–8 weeks, although they may occur later or after treatment discontinuation [4–8].

As most patients show primary or adaptive resistance to monotherapy, the use of combinations of ICIs [9] and other drugs (e.g., chemotherapy and tyrosine kinase inhibitors [TKIs]) is rapidly expanding, albeit at the cost of increased toxicity. Present guidelines, based on results from retrospective studies of ICI-induced diarrhea/colitis, recommend a universal approach for management [10]. Accordingly, a risk estimation of intestinal complications across various ICIs and combination regimens is essential to optimize treatment.

This systematic review and meta-analysis focused on the incidence of
ICI-induced diarrhea and colitis with monotherapy, combination therapy, as well as pathology, and management hereof.

Methods

Registration

The study protocol was registered in the international prospective register of systematic reviews PROSPERO on May 20, 2020 (ID CRD42020187473).

Data sources and searches

This systematic review was performed following the Cochrane Handbook for Systematic Reviews of Interventions and PRISMA guidelines [11–14] (Suppl. Table 1). We performed two separate literature searches on Medline, Embase, and Central (Studies I, Iia and Iib (studies for Iia and b were performed in one search strategy)). In our search, no restrictions on language or publication date were applied. Search strategies are shown in the Supplement.

Screening was performed independently by two authors (DLN and OHN). Full-text articles were obtained from the relevant records and reviewed for eligibility. Disagreements regarding eligibility were discussed with the coauthors until a consensus was reached.

Study selection

Inclusion criteria for Study I were adult patients with malignancies treated with ICIs approved by the U.S. Food and Drug Administration (FDA) or European Medicine Agency (EMA), phase I-IV trials, and data on diarrhea and/or colitis. When several publications existed on the same study, we extracted all available data from the different publications. Studies without new safety data were excluded. Case reports, retrospective analyses, letters, reviews, and editorials were also excluded. Furthermore, escalation studies, studies with < 10 patients in each group or several doses reported together, and studies on intratumoral injection were excluded. For Study Iia, all studies describing histopathologic and endoscopic findings in the GI tract among patients with ICI-induced colitis were included. For Study Iib, phase I-IV or retrospective studies (≥5 patients) of biologic treatment (e.g., tumor necrosis factor [TNF] monoclonal antibodies [15]/monoclonal antibodies to the bowel-specific α4β7-integrin [16]) in patients with ICI-induced colitis were included. Furthermore, for Study Iib, conference abstracts were included if no full-length articles were available. Reference lists from the articles were screened for relevant studies. Only studies published in English were included.

Data extraction

The following data were extracted independently: Study I (DLN and IMC): first author, publication year, interventions, tumor type, phase, National Clinical Trial (NCT) number, number of patients, duration of treatment, follow-up, diarrhea/colitis (treatment-related adverse event [TRAE] grade 1–4 and grade 3–4), death due to diarrhea/colitis, discontinuation due to toxicity, specifications concerning adverse event reporting, and treatment of side effects. Study Iia (OHN and LK): first author, publication year, number of patients, histology grading system applied, and conclusions dealing with pathology depicted. For Study Iib (OHN and DLN): first author, publication year, intervention, phase, NCT number, number of patients, tumor type and ICI, patient characteristics (prednisolone exposure, prior biologic therapy), diagnostic criteria, number of doses, and efficacy (remission rate).

Assessment of risk of bias

The risk of bias was assessed in Study I independently by DLN and OHN. For Study Iia and Iib, the risk of bias was assessed using the McMaster Quality Assessment Scale for Harms [17]. No quality assessment was performed for Study Iia. The Newcastle-Ottawa Quality Assessment was conducted independently by DLN and OHN for Study Iib [18]. Controversies were resolved via discussion with the coauthors.

Pharmacovigilance databases

Data concerning colitis, enterocolitis and intestinal perforation registered by May 30, 2021 were collected from in VigiLyze (integrated with the global adverse drug reaction database VigiBase), EudraVigi-lance (system for managing and analyzing information on suspected adverse reactions to medicines that have been authorized or are being studied in clinical trials in the European Economic Area, operated by the EMA), and FAERS (FDA Adverse Event Reporting System) databases.

Statistical analysis

Incidences of diarrhea/colitis were calculated with 95% Confidence Intervals (CIs) using the metaprop command in STATA 17.1 (StataCorp, College Station, TX) and by applying the Freeman–Tukey double-arcsine transformation to control for studies with no events. To explore the difference between ICIs in the incidence of diarrhea/colitis, a random-effects meta-analysis was performed, assuming heterogeneity due to differences in participants and diseases. Heterogeneity was evaluated by assessing the I² statistics as the percentage of variance attributable to inconsistencies. Differences between the incidences of different ICIs were assessed using Cochran’s Q test. Because of multiple testing, a significance level of 0.001 was applied when comparing the incidence of GI toxicity for individual ICIs.

Results

Incidence of diarrhea and colitis

Eight ICIs are currently approved for clinical use by the FDA and EMA (Suppl. Table 2). Our search, updated April 21, 2021, identified 6,860 records. In total, 434 full-text articles met our inclusion criteria, representing 411 unique studies, and 316 studies were included in the meta-analysis (some studies were included in several analyses; Suppl. Fig. 1). The studies are listed in Suppl. Table 3 (A-G). In general, ICIs targeting PD-1/PD-L1 have been combined with every conceivable drug category. Toxicity was manageable; however, there are a few exceptions. Three studies were terminated because of liver toxicity [19–21], and one study was discontinued because of interstitial lung disease [22].

In total, 397 studies used the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4 or 5, for grading toxicity [23]. In ten studies, findings were unclear or the version was not specified; only four studies did not use NCI-CTCAE for reporting adverse events (AE). Nonetheless, the grading of diarrhea and colitis was similar between the two CTCAE versions (Suppl. Table 4). The risk of bias and methodological quality is displayed and summarized in Suppl. Tables 5 (A-G) and 6. In general, the quality of the included studies was high.

Incidence of Diarrhea/Colitis associated with PD-1 inhibition

The incidences of diarrhea and colitis are shown in Fig. 1 and Suppl. Table 7. The incidence of grade 1–4 and grade 3–4 diarrhea after a 200 mg dosage of pembrolizumab every three weeks (Q3W; the standard dose) was 9.5% and 0.3%, respectively, whereas the incidence of grade 1–4 and grade 3–4 colitis was 1.3% and 0.4%, respectively.

Studies investigating the standard flat dose of nivolumab (240 mg; Q2W) reported incidence of grade 1–4 and grade 3–4 diarrhea of 11.6% and 0.4%, respectively. The incidence of grade 1–4 and grade 3–4 colitis was 0.2% and 0.0%, respectively. The current recommended dose of 480 mg Q4W was part of the intervention of eight studies [24–31].
Cemiplimab was investigated in three studies, including two dose regimens (3 mg/kg Q2W or 350 mg Q3W). The overall incidence of grade 1–4 and grade 3–4 diarrhea was 11.5% and 0.04%, respectively, and the incidence of grade 1–4 and grade 3–4 colitis was 0.8% and 0.04%, respectively. The overall incidence of grade 1–4 and grade 3–4 diarrhea following treatment with a PD-1 inhibitor was 10.7% and 0.2%, respectively, and the incidence of grade 1–4 and grade 3–4 colitis was 1.2% and 0.2%, respectively (Fig. 2 and Suppl. Table 8). Four deaths due to colitis were recorded in the 19,715 patients (one study did not report cause of death (1008 patients [32])). The discontinuation rate due to occurrence of diarrhea, grade 1–4

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**Diarrhea, grade 1–4**

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**Diarrhea, grade 3–4**

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<tr>
<td>PD-L1</td>
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**Colitis, grade 1–4**

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**Colitis, grade 3–4**

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<td>180</td>
<td>17802</td>
<td><strong>23.5</strong></td>
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</tbody>
</table>
diarrhea and/or colitis was 6.1%.

**Incidence of Diarrhea/Colitis associated with PD-L1 inhibition**

The incidences of diarrhea and colitis are shown in Fig. 1 and Suppl. Table 7. The incidence of grade 1–4 and grade 3–4 diarrhea following a 1,200 mg dosage of atezolizumab Q3W was 8.8% and 0.1%, respectively, whereas the incidence of grade 1–4 and grade 3–4 colitis was 0.6% and 0.3%, respectively.

The incidence of grade 1–4 and grade 3–4 diarrhea after the currently recommended flat dose of 1,500 mg of durvalumab Q4W was 6.1% and 0.0%, respectively. Grade 1–4 and grade 3–4 colitis were reported with an incidence of 0.2% and 0.06%, respectively.

For nivolumab, the incidence of grade 1–4 and grade 3–4 diarrhea was 6.7% and 0.0%, respectively, whereas the incidence of grade 1–4 and grade 3–4 colitis was 0.2% and 0.0%, respectively.

The overall incidence of grade 1–4 and grade 3–4 diarrhea after treatment with a PD-L1 inhibitor was 8.0% and 0.02%, respectively, and the overall incidence of grade 1–4 and grade 3–4 colitis was 0.3% and 0.04%, respectively (Fig. 2 and Suppl. Table 8). Among 10,035 treated patients, two deaths due to colitis were recorded (one study did not report cause of death (237 patients [33])). The discontinuation rate due to diarrhea and/or colitis was 5.4%.

**Incidence of Diarrhea/Colitis associated with PD-1/PD-L1 monotherapy**

A comparison of the incidence of diarrhea/colitis after PD-1 and PD-L1 inhibition showed that the incidence of diarrhea grade 1–4 (10.6% vs 8.0%, P < 0.002), diarrhea grade 3–4 (0.2% vs 0.02%, P < 0.002), and colitis grade 1–4 (1.2% vs 0.3%, P < 0.001) were significantly higher for PD-1 inhibitors. However, the incidence of colitis grade 3–4 (0.2% vs 0.04%, P = 0.143) did not differ between the compounds. Furthermore, findings for the individual compounds were inconsistent, and the differences did not seem to be clinically relevant (Suppl. Table 9).

**Incidence of Diarrhea/Colitis associated with CTLA-4 inhibition**

The incidence of diarrhea/colitis following ipilimumab treatment differed significantly between the doses (Fig. 1 and Suppl. Table 7). Grade 1–4 and grade 3–4 diarrhea after a 3 mg/kg dosage of ipilimumab was 28.6% and 5.9%, respectively, with the incidence of grade 1–4 and grade 3–4 colitis at 11.2% and 4.9%, respectively. Nine deaths due to fulminant colitis/intestinal perforation were recorded in 2,387 patients (cause of death reported in all studies). Thus, the incidence of diarrhea/colitis associated with a CTLA-4 inhibitor was significantly higher than that associated with PD-1/PD-L1 monotherapy (P < 0.001 for all analyses).

**Incidence of Diarrhea/Colitis associated with PD-1/PD-L1 inhibition in combination with ipilimumab**

The incidence of grade 1–4 and grade 3–4 diarrhea after a 3 mg/kg dosage of nivolumab and a 1 mg/kg dosage of ipilimumab Q3W, the currently recommended doses [34] for renal cell carcinoma and colorectal cancer, was 21.0% and 2.7%, respectively, whereas the incidence of grade 1–4 and grade 3–4 colitis was 3.6% and 1.2%, respectively. For a 1 mg/kg dosage of nivolumab and a 3 mg/kg dosage of ipilimumab Q3W, the currently recommended doses for melanoma [34] and hepatocellular carcinoma [35], the incidence of grade 1–4 and grade 3–4 diarrhea was 36.6% and 7.4%, respectively, whereas the incidences of grade 1–4 and grade 3–4 colitis were 8.2% and 5.6%, respectively. Compared with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, the incidence of severe colitis was significantly higher for nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (P = 0.001; Fig. 3 and Suppl. Table 10). Finally, nivolumab 3 mg/kg Q3W and ipilimumab 1 mg/kg Q6W has been approved by FDA for treatment of non-small cell lung cancer [36]. The incidence of grade 1–4 and grade 3–4 diarrhea was 20.3% and 1.6%, respectively, whereas the incidences of grade 1–4 and grade 3–4 colitis were 4.7% and 2.7%, respectively.

For all combinations, the incidence of diarrhea and colitis was significantly higher than that of PD-1/PD-L1 inhibitors (P < 0.001), whereas the incidence of grade 5 events did not increase (cause of death reported in all studies).

**Incidence of Diarrhea/Colitis associated with PD-1/PD-L1 inhibition in combination with chemotherapy**

The incidence of all grade of diarrhea was approximately three times higher following treatment with a PD-1 inhibitor in combination with platin-based chemotherapy than for monotherapy (29.3%). Furthermore, the incidence of grade 3–4 diarrhea increased significantly (2.2%). The incidence of grade 1–4 and grade 3–4 diarrhea after platin-based chemotherapy alone in randomized trials ranged from 19% to 24% and 0% to 3%, respectively [37–40]. The incidence of grade 1–4 and grade 3–4 colitis following a PD-1 inhibitor plus platin-based chemotherapy was 1.6% and 0.6%, respectively (Fig. 4 A, Suppl. Tables 11 and 12).

The incidence of diarrhea/colitis following a PD-L1 inhibitor in combination with platin-based chemotherapy was comparable to that of PD-1 inhibitors in combination with platin-based chemotherapy (Fig. 4 A, Suppl. Tables 11 and 12).

Few studies investigated taxane-based treatment. Following combination therapy with PD-1/PD-L1 inhibitors (5 studies each) and taxane-based chemotherapy, the incidence of grade 1–4 diarrhea was higher than that for combinations with platin (37%-40%). However, the incidences of severe diarrhea (approximately 2%) and colitis grade 3–4 (<0.5%) were low (Fig. 4 B, Suppl. Tables 13 and 14).

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**Forest plot of incidences of any grade diarrhea and colitis and grade 3–4 diarrhea and colitis following PD-1 inhibitor and CTLA-4 inhibitor therapy (nivolumab and ipilimumab).**

![Forest plot of incidences of any grade diarrhea and colitis and grade 3–4 diarrhea and colitis following PD-1 inhibitor and CTLA-4 inhibitor therapy (nivolumab and ipilimumab).](image-url)
Incidence of Diarrhea/Colitis associated with PD-1/PD-L1 inhibition in combination with other drugs

Totally, 12 studies, including 1478 patients, investigated the combination of a PD-1/PD-L1 inhibitor and a TKI targeting angiogenesis (regorafenib/sunitinib (3 studies); lenvatinib/axitinib (9 studies)) (Suppl. Table 16). A high incidence of grade 1–4 (37%-54%) and grade 3–4 diarrhea (up to 9%) [41,42] was reported for these combinations. However, the incidence of colitis of grade 1–4 was low (approximately 2%). Diarrhea seemed to be much less frequent when PD-1/PD-L1 inhibitors were combined with bevacizumab (16%) (7 studies; 1152 patients) (Suppl. Table 16) [43]. Only few studies evaluated the combination of an ICI and TKI aimed for other targets. The combination of a PD-1/PD-L1 inhibitor and a TKI targeting epidermal growth factor receptor (EGFR) has only been investigated in three small studies including 44 patients [21,22,44]. The combination was followed by grade 1–4 diarrhea in 29% of patients with low incidence of severe diarrhea/colitis (3%). Finally, ICI in combination with the anaplastic lymphoma kinase (ALK) inhibitors, crizotinib or ceritinib, has been evaluated in one study including 49 patients [45]. The incidence of grade 1–4 diarrhea was 52%, whereas only one event of grade 3–4 diarrhea was reported in the ceritinib arm (1%) (Suppl. Table 16). Independent of treatment modality, the incidence of diarrhea seemed to be additive with no clinically relevant increase in the incidence of colitis.

A

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B

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</table>

Fig. 4. Forest plot of incidence of any grade diarrhea and colitis and grade 3–4 diarrhea and colitis following PD-1 and PD-L1 inhibitor therapy in combination with platin-based (A) and taxane-based chemotherapy (B).

An overview from pharmacovigilance databases

We collected data concerning colitis and intestinal perforation in VigiLyze, EudraVigilance, and FAERS databases registered by May 30, 2021 (Suppl. Table 17). Microscopic colitis was registered for all drugs except avelumab, which was probably due to a limited number of cases [46]. Microscopic colitis accounted for 1%-3% of all reported colitis cases following PD-1/PD-L1 inhibitors, whereas the condition during treatment with ipilimumab accounted for 0.4%-0.7%. Fatal events and intestinal perforation were reported for all ICIs, however, most frequently reported with ipilimumab (Suppl. Table 17).

Histopathology

For Study IIa, 23 studies reporting on a total of 902 cases of biopsy-proven histopathologic changes in colitis induced by ICI therapy were identified (Suppl. Fig. 2 and Suppl. Table 18) [4,47–68]. Due to the large differences between study design and reporting methodology, a meta-analysis was not performed.

Endoscopic features

ICI-induced colitis may affect the entire colon or only segments and abnormal endoscopic findings can be either diffuse or patchy [57]. In general, erosions and ulcerations at endoscopy are indicative of
histopathologic findings of inflammation, although biopsies from a normal endoscopy may reveal both acute and chronic changes [55]. Associated diffuse enteritis was present in one-quarter of patients and may occur even in the absence of any endoscopic findings of colitis [69].

**Microscopic features**

The most common histopathological findings were increased mixed lymphoplasmacytic infiltrates in the lamina propria, and varying degrees of neutrophilic infiltration in the epithelium and crypts. Based on the large overlap between microscopic findings of other known types of colitis, ICI-induced colitis has been grouped into different histopathologic patterns [57,61,70] (Table 1), namely: (1) acute active colitis, (2) chronic active colitis, (3) microscopic colitis-like, (4) graft-versus-host disease-like, and (5) other types (i.e., mixed type, ischemic colitis-like, nonspecific inflammatory reactive changes).

The most common pattern in the 902 cases was acute active colitis (44%), followed by chronic active colitis (32%), indicating that active inflammation with neutrophils was present in a minimum of 76% of cases (Suppl. Table 19). The inflammatory infiltrates were diffuse in the majority of cases and less often focal or patchy [50,54,61]. Microscopic colitis with a predominance of the lymphocytic-like pattern was reported in 14% of cases. Only few studies have reported on the correlation between ICI type and specific histopathologic changes. Two studies found no correlation [4,64], but others reported that patients treated with anti-CTLA-4 were more likely to have acute active colitis and less likely to have chronic and microscopic colitis [61]. The fractions of cases with a specific histopathologic pattern related to type of ICI treatment in all 902 cases are found in Suppl. Table 19, although not all studies specified whether the histopathologic changes were related to PD-1 and CTLA-4 as mono- or combination therapy. No data for PD-L1 as mono-therapy, combinations with chemotherapy or TKIs were identified.

None of the histopathological features reported for ICI-induced colitis were, however, specific. The acute colitis pattern showed similarities with acute intestinal infections and drug-induced colitis, whereas the active chronic colitis pattern shared features with inflammatory bowel disease (IBD) [54,61]. Compared with ulcerative colitis, the number of apoptosis was higher in ICI-induced colitis [49]. The severity of inflammatory damage may predict clinical outcome [48,62]. Though, as with other types of colitis, the correlation between symptoms and endoscopic and histologic findings has been found to be only modest [4]. No consensus on the histopathologic grading of ICI-induced colitis exists; however, scoring indexes designed for inflammatory bowel disease can be used although they might not be fully feasible [71–73]. Thus, both the Nancy Index and Roberts Histopathologic Index have been applied in retrospective analyses and were independently associated with the use of biologics and adverse ICI-induced colitis outcomes [55,64]. Nonetheless, these findings need to be validated in prospective studies.

**Therapy of ICI-induced colitis**

For glucocorticoid-refractory cases with CTCAE grade 2 or higher diarrhea or colitis, guidelines recommend biologics at an early point with either infliximab (TNF inhibitor [15]) or vedolizumab (α4β7 anti-integrin [74]) [75–78]. To assess the efficacy of biologics, we identified 25 records (Suppl. Fig. 2): 20 publications with infliximab [4,48,59,60,65,68,79–92], three with vedolizumab [74,93,94], and two with both [95,99], including 613 patients (Suppl. Table 20). The risk of bias and methodological quality is displayed in Suppl. Table 21. In general, the quality of the included studies was good.

Measured by clinical remission of symptoms, infliximab (5 mg/kg) was efficient in 87% of patients (95% CI 79% to 94%; 502 patients) and vedolizumab in a flat-dose regimen of 300 mg in 88% of patients (95% CI 62% to 100%; 111 patients) without any significant differences (P = 0.96; Fig. 5). Notably, biologics do not necessarily follow the same dosage regimens used for IBD [15,96], because shorter intervals between dosages may be considered on a case-by-case basis for ICI-induced colitis [97]. In patients failing an immunobiological agent, a shift out-of-class (i.e., TNF inhibitor versus anti-integrin) seems reasonable, and of notice no biomarkers predicting the therapeutic response have so far been identified.

In the case of ICI-induced microscopic colitis [70], budesonide appears to be efficient [84], although data suggest that a more aggressive disease course may require potent immunomodulatory treatment regimens [98].

**Discussion**

To our knowledge, this is the largest and most comprehensive analysis to evaluate the lower GI side effects of ICIs. We found that the incidence of anti-PD-1/PD-L1 antibody-induced diarrhea and colitis was 10% and 2%, respectively, whereas the incidence of diarrhea and colitis after ipilimumab treatment was 33%-50% and 7%-22%, respectively. The incidence of diarrhea and colitis of all grade were significantly higher for PD-1 inhibitors. However, the incidence of colitis grade 3–4 did not differ between the PD-1 and PD-L1 inhibitors. In addition, findings for the individual compounds were inconsistent, and the differences did not seem to be clinically relevant. Our findings might be explained by the different dose regimens included in the analysis. Thus, whether the incidence and severity of PD-1/PD-L1-induced diarrhea/colitis are dose dependent is unclear. In the present study the incidence of pembrolizumab-induced diarrhea grade 1–4 was dose dependent (data not shown). However, grade 3–4 diarrhea and colitis were not different between cohorts. In contrast, a meta-analysis of TRAEs related to different ICIs found atezolizumab 1,200 mg and pembrolizumab 2 mg/kg every 3 weeks being safer than other ICIs [99]. A high incidence of colitis was observed after ipilimumab in combination with nivolumab, with colitis occurring in 4%-8% of patients depending on regimen. For all combinations, the incidence of diarrhea and colitis was significantly higher than that of PD-1/PD-L1 inhibitors reflecting the general increased incidence of (severe) irAEs in patients receiving chemotherapy in combination with ICIs [100]. Platinum and taxane compounds were used in several different combinations. Besides, several platin-based studies did not report type of drug [37,40,101,102].

**Table 1**

<table>
<thead>
<tr>
<th>Histopathologic pattern</th>
<th>Typical microscopic findings</th>
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<tbody>
<tr>
<td>Acute active colitis</td>
<td>Cryptitis (intraepithelial neutrophils)</td>
</tr>
<tr>
<td></td>
<td>Crypt abscesses (neutrophils in crypt lumen)</td>
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<tr>
<td></td>
<td>Crypt atrophy and dropout</td>
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<tr>
<td></td>
<td>Increased intraepithelial lymphocytes</td>
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<tr>
<td></td>
<td>Increased epithelial apoptosis can be present</td>
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<tr>
<td>Chronic active colitis</td>
<td>Findings of active colitis</td>
</tr>
<tr>
<td>“IBD-like”</td>
<td>Basal plasmacytosis</td>
</tr>
<tr>
<td></td>
<td>Crypt architectural distortions</td>
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<tr>
<td></td>
<td>Paneth cell metaplasia</td>
</tr>
<tr>
<td></td>
<td>Mucin depletion</td>
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<tr>
<td></td>
<td>Granulomas is relation to ruptured crypts</td>
</tr>
<tr>
<td>Microscopic colitis</td>
<td>More than 20 intraepithelial lymphocytes per 100 epithelial cells</td>
</tr>
<tr>
<td>Lymphocytic colitis</td>
<td>A thickened subepithelial collagenous band &gt; 10 μm</td>
</tr>
<tr>
<td>“GVHD-like”/apoptosis</td>
<td>Increased number of crypt epithelial apoptosis without features of acute or chronic inflammation</td>
</tr>
<tr>
<td>only</td>
<td>Withered crypts</td>
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<tr>
<td></td>
<td>Reactive epithelial changes</td>
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<tr>
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<td>Lamia propria fibrosis</td>
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IBD, inflammatory bowel disease; GVHD, graft versus host disease.
Thus, it was impossible to summarize findings to differentiate between the compounds. However, the prevalence of diarrhea after cisplatin or carboplatin has previously been reported to be low [103]. In addition, a retrospective recent study including 36,595 patients receiving platin-based chemotherapy found that only 0.2% developed endoscopic confirmed diarrhea and colitis independent of the drug used [104]. For patients receiving treatment with a taxane, all grade diarrhea has been reported in approximately 40% of patients independent of drug used [103]. However, whereas no patients receiving nab-paclitaxel have been reported to have ≥ grade 3 toxicity, 0–27% of patients receiving docetaxel, and 3–7% of patients receiving paclitaxel had ≥ grade 3 diarrhea. Moreover, cases of severe colitis have been reported.

When ICIs were combined with other agents, the incidence of diarrhea seemed to be additive, with up to 56% reported after combinations with TKIs. The influence of combination therapy on the frequency of colitis was minor and did not seem to be clinically relevant.

Three main patterns of histopathologic presentation were identified: acute active colitis, chronic active colitis, and microscopic colitis-like. Despite the wide use of ICIs and relatively frequent GI AEs, no published prospective studies investigating the (optimal) biologic treatment of ICI-induced colitis and only a few ongoing studies (Suppl. Table 22) were identified. Current guidelines recommend infliximab or vedolizumab for persistent diarrhea/colicitis grade 2 and grade 3–4 (Suppl. Table 23). In our meta-analysis, infliximab and vedolizumab were equally effective, supporting this strategy. However, prospective studies are required to determine whether any subgroup may benefit from more specific treatment options. Thus, evidence suggests the launching of a paradigm shift toward more selective management of high-grade ICI-induced colitis using biologics as first-line therapies [95]. This strategy has the potential to prevent the development of a chronic inflammatory state and to avoid interruption of ICI treatment [95]. Moreover, the potential synergistic effect of TNF inhibitors and ICIs has been suggested [106–108], and this strategy is currently being investigated in the TICIMEL trial (NCT03293784) (Suppl. Table 22).

The biologic tocilizumab, an IL-6 receptor antagonist, a key drug in rheumatoid arthritis [109], has shown clinical efficacy in 79% of the cohort in a retrospective study including 34 patients with a grade 3–4 irAE (pneumonitis, 35%; serum sickness, 35%; colitis, 3%) [110]. In addition, tocilizumab has been investigated in patients with ICI-induced colitis (COLAR trial; 19 patients with colitis/arthritis) in a preliminary study published after our final search of April 21, 2021 [111]. The authors concluded that tocilizumab showed promising clinical efficacy in the treatment of ICI-induced arthritis and/or colitis, as 80% of patients with colitis had ≥ 1 grade improvement in symptoms. Lastly, case reports with ustekinumab (2 cases), an IgG1k monoclonal antibody that binds with specificity to the p40 protein subunit of IL-12 and IL-23 [112], and the small molecule tofacitinib (4 cases), a pan-JAK inhibitor [113], have shown promise as alternatives to existing therapy, whereas the TNF inhibitor adalimumab has not been successful for ICI-induced colitis [88]. Nonetheless, larger investigations with a sufficient number of observations are warranted.

Treatment guidelines support the early use of glucocorticoids for ICI-induced diarrhea/colicitis (Suppl. Table 23) [75–77,105,114]. In general, data on the treatment of side effects are missing from clinical trials (Suppl. Table 3). Recent data have indicated that glucocorticoids may be associated with a potential risk of impaired antitumor efficacy [115,116], but prospective data are still awaited. A meta-analysis, including 4,045 patients, showed that although glucocorticoids used to...
colonoscopies; thus, the challenge is to distinguish between glucocorticoids and/or require a huge number of assessments, including colonoscopies; thus, the challenge is to distinguish between chemotherapy/TKI and ICI-induced diarrhea. Therefore, a more individualized and tailored approach for patients with low-grade diarrhea is suggested. In patients with diarrhea ≤grade 2 and without abdominal symptoms as pain, bleeding etc., we suggest a more conservative approach with loperamide, hydration, and close monitoring, only initiating glucocorticoids in case of worsening or persistent symptoms.

Detailed endoscopic and histologic information is critical to obtain an accurate assessment of ICI-related toxicity and to make more informed decisions on treatment. Thus, timely identification may result in treatment initiation at an early point [48], thereby decreasing the rate of progression to severe flares and hospitalizations [95]. However, as stated above, this might require a large number of (invasive and costly) colonoscopies. Inflammatory biomarkers, including fecal lactoferrin and calprotectin, used as surrogate markers in patients with IBD, have demonstrated early promise. Given a similar pathophysiology process one may presume the role of these inflammatory biomarkers in patients with ICI-induced colitis. Currently, only few studies have been performed in patients with ICI-induced colitis. A study has shown that low fecal calprotectin levels at symptom onset was associated with a higher clinical response rate. Furthermore, patients with clinical responses had lower post-treatment calprotectin levels [118]. In another study, patients who achieved endoscopic remission after treatment had a significantly lower calprotectin concentration at symptom onset and after treatment compared with those without endoscopic remission [119]. Thus, a simple stool test may be a novel tool for screening patients with diarrhea or colitis and stratifying patients who will need an endoscopy. Thus, inflammatory biomarkers have started to be incorporated into guidelines [118,120–122]. Nevertheless, prospective validation is required [121,123].

To distinguish between chemotherapy/TKI and ICI-induced diarrhea, as well as to identify patients with microscopic colitis (approxi-


control cancer-related symptoms were associated with a negative effect on overall mortality, glucocorticoids used to mitigate adverse events did not negatively affect overall mortality [117].

Guidelines are based on expert experience and (small) observational studies, including patients who develop diarrhea/colitis following ICI monotherapy, primarily ipilimumab, or combinations of ICIs. Currently, several combinations of ICIs and chemotherapy or TKIs have been approved by the FDA and EMA, and combination therapy is the standard treatment for many cancers, such as non-small cell lung cancer, head and neck squamous cell carcinoma, gastric and esophageal cancer, and renal cell carcinoma. The incidence of all-grade diarrhea following such regimens was in our analysis additive and (very) high (17%-40% for chemotherapy and up to 56% for TKIs). In contrast, the incidence of grade 3–4 events was limited (around 2%) and the risk of severe colitis was low (approximately 0.5%), although colon perforation and fatal colitis-related events have been reported for all ICIs (Suppl. Table 17).

The current guidelines (Suppl. Table 23) might result in the overuse of glucocorticoids and/or require a huge number of assessments, including colonoscopies; thus, the challenge is to distinguish between chemotherapy/TKI and ICI-induced diarrhea. Therefore, a more individualized and tailored approach for patients with low-grade diarrhea is suggested. In patients with diarrhea ≤grade 2 and without abdominal symptoms as pain, bleeding etc., we suggest a more conservative approach with loperamide, hydration, and close monitoring, only initiating glucocorticoids in case of worsening or persistent symptoms.

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To distinguish between chemotherapy/TKI and ICI-induced diarrhea, as well as to identify patients with microscopic colitis (approximately 10% of patients) who can be treated with budesonide, a colonoscopy with biopsy should (still) be mandatory for all patients with persistent grade 2 diarrhea and patients with grade 3–4 diarrhea.

Our study has several strengths. We employed a rigorous and comprehensive literature search focusing on both oncologic and hemato-


ticologic patients. Only two studies were excluded because of missing data (i.e., only reporting TRAEs ≥10% or 15% and reporting no AEs; 304 patients) [24,121]. All TRAEs and AEs from different parts of the world were included, broadening the generalizability of our findings. Our meta-analysis included several studies with relatively large datasets, which increased statistical power. Moreover, to our knowledge, this is the first and largest study of all grades of GI toxicity to include combination therapy. However, our study had some limitations. Study I included all identified phase I-IV studies reporting AEs in English, except for studies with escalation or <10 patients. Overall, 397 of the 411 studies used a specific version of the NCI-CTCAE. Thus, sensitivity analyses restricted to studies using the CTCAE were not performed. Because most studies only reported data on TRAEs and/or irAEs, we chose to use these data instead of data on AEs; thus, we may have underestimated the incidence of diarrhea/colitis. In addition, all studies in Study II investigating colitis therapy were retrospective, the number of patients was limited, and the criteria for inclusion of patients were heterogeneous. The identification of these studies depended on indexed terms regarding (entero-)colitis; thus, we may have missed some studies.

Finally, it should be noted that the evaluation tool for diarrhea/colitis was based on CTCAE classification, solely relying on clinical symptoms and signs, which classifies diarrhea and colitis into grades 1–5 depending on severity [75,76]. In clinical practice, however, endoscopic evaluations with biopsies are performed on a case-by-case basis but are not specified in the CTCAE diagnosis and severity assessment. CTCAE (Suppl. Table 4) for diarrhea and colitis have been used interchangeably in most of the published literature, creating some confusion when discussing ICI-related GI toxicities. It is difficult to distinguish these conditions because they frequently overlap and may represent different levels of complications. Therefore, most recommendations for management are based on a combination of clinical symptoms and endoscopic signs, which in many cases are not the same.

Conclusions

No clinically meaningful differences in the incidence of immune-mediated colitis were found between PD-1 and PD-L1 inhibitors. However, colitis was more prevalent with anti-CTLA-4 therapy and ICI combinations. The incidence of all-grade diarrhea following ICI in combination with chemotherapy or TKIs was high, whereas only a few patients developed colitis. For these settings, we suggest a more tailored and individualized approach to managing patients with low-grade diarrhea. A more comprehensive grading system is warranted to incorporate the clinical signs and symptoms and the endoscopic and histologic components, similar to systems that are well established for IBD, such as the SCCAI [126] or Mayo score [127]. Currently, no studies have yet investigated histopathologic findings after ICI in combination with chemotherapy or TKIs. Adequately powered prospective clinical trials, including quality of life and cost-effective analyses, are needed to confirm the abovementioned hypotheses and to validate potential biomarkers of inflammation and refine management.

Additional information

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Author Contributions

DLN had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: DLN, CBJ, IMC, and OHN.

Acquisition, analysis, or interpretation of data: DLN, CBJ, IMC, JK, and OHN.

Drafting of the manuscript: DLN, CBJ, IMC, JK, and OHN.

Critical revision of the manuscript for important intellectual content: DLN, CBJ, IMC, JK, and OHN.

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NA.

Declaration of Competing Interest
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Appendix A. Supplementary material
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