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Infection risk with PI3K-AKT-mTOR pathway inhibitors and immune checkpoint inhibitors in patients with advanced solid tumours in phase I clinical trials

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ABSTRACT

Background Patients undergoing chemotherapy are known to be at risk for infection from myelosuppression by cytotoxic agents (CTAs) or immunosuppressive effects from mTOR inhibitors. The infection risk of newly developed anticancer agents has not been fully evaluated. It remains unknown how T-cell activation induced by immune checkpoint inhibitors (ICIs) relates to infection.

Methods We retrospectively examined infection risk in patients with cancer treated with investigational agents in a phase I study. The investigational agents were classified into four groups: CTA, phosphatidylinositol 3 kinase/Akt/mammalian target of rapamycin inhibitor (PAM), molecular targeted agent (MTA) and ICI. All infection-related adverse events (AEs) during treatment were recorded. We compared the CTA, PAM and ICI with MTA, because MTA are already considered low risk and were used in the largest number of patients.

Results A total of 641 patients were enrolled: 35 CTAs (5.5%), 61 PAMs (9.5%), 445 MTAs (69.4%) and 100 ICIs (15.6%). Among all patients, 132 (20.6%) experienced infection-related AEs and 46 (7.2%) developed 50 ≥grade 3 infection-related AEs. In any infection-related AEs, the ORs compared with MTAs were 2.19 (95% CI 1.03 to 4.66) for CTAs, 3.55 (95% CI 2.02 to 6.24) for PAMs and 1.05 (95% CI 0.60 to 1.85) for ICIs, respectively. In time to the first infection-related AE analysis, the risks for any infection-related AE from CTAs and PAMs were higher than those from MTAs (HR 1.84 (95% CI 0.82 to 4.11); p=0.05 and 3.96 (95% CI 2.18 to 7.22); p<0.001). The risk from ICIs was not significantly different from that of MTAs (HR 0.71 (95% CI 0.46 to 1.10); p=0.19).

Conclusion Our results validate that PAMs and CTAs carry a higher infection risk in patients with advanced solid tumours compared with MTAs. We suggest that the infection risk of ICIs is a similar infection risk to MTAs.

Key questions

What is already known about this subject?

- Patients with cancer undergoing cytotoxic chemotherapy are at risk for infection caused by myelosuppression.
- Phosphatidylinositol 3 kinase/Akt/mammalian target of rapamycin (PAM) inhibitors have immunosuppressive effects and have been shown to increase the risk of infection in patients with renal cell carcinoma.
- It remains unknown how T-cell activation induced by immune checkpoint inhibitors reduces the risk of infection.

What does this study add?

- Our results validate that PAM inhibitors and cytotoxic agents carry a higher infection risk in patients with a variety of advanced solid tumours compared with molecular targeted agents.
- Immune checkpoint inhibitors conferred an infection risk in patients with solid tumours similar to that of molecular targeted agents.

How might this impact on clinical practice?

- Intense infection control and prevention should be practised during treatment with PAM inhibitors.
- Immune checkpoint inhibitors have a similar infection risk compared with molecular targeted agents.

INTRODUCTION

Patients with cancer undergoing chemotherapy are at risk for infection. Cytotoxic agents (CTAs) induce myelosuppression, including neutropenia, which weakens host defence against infection. The risk of infection during CTA chemotherapy is well known to increase with the degree and duration of neutropenia.[1 2] On the other hand, molecular targeted agents (MTAs), including small molecules and monoclonal antibodies, interfere with a specific molecular target involved in tumour growth and progression, and most of their side effects are directly related to the specific molecular target in normal tissues inhibited or modulated by the specific drug.[3] Therefore, most MTAs are generally considered to confer a low risk for infection caused by leucopenia and neutropenia.[4 5]

Phosphatidylinositol 3 kinase/Akt/mammalian target of rapamycin (PAM) is a critical signalling pathway that controls cell cycle, survival, metabolism, motility and genomic stability.[6 7] Its alterations in cancer cells include somatic amplification, mutation, loss of heterozygosity and changes in DNA methylation. New anticancer agents targeting this pathway have been developed for the treatment of various malignancies.[8–10] PI3K inhibitors, including idelalisib, copanlisib and duvelisib have been approved in the USA for the treatment of chronic lymphocytic leukaemia and a specific type of lymphoma. mTOR inhibitors, including everolimus and temsirolimus, are approved for the treatment of some malignant solid tumours such as renal cell cancer, neuroendocrine tumours and breast cancer. Most PAMs are still under investigation. The PAM pathway in normal cells plays an important role in cell growth, regulation of blood glucose homeostasis and lipid metabolism and regulation of the immune system and cytokine production by immune cells. Based on a different mechanism from classical myelosuppression, PAMs have immunosuppressive effects and have been shown to increase the risk of infection.

Recently, the clinical success of immune checkpoint blockade has brought about dramatic breakthroughs in oncology. Immune checkpoint inhibitors (ICIs) such as cytotoxic T-lymphocyte antigen-4, programmed cell death protein-1 (PD-1) and its ligand, programmed death-ligand 1 target downregulators of the anticancer immune response, unleashing the host immune reaction against tumour cells by T-cell activation. Many immune-related adverse events have been reported; these most often occur as the immune system becomes less suppressed and affect various organs, including the gastrointestinal tract, where they cause diarrhoea and colitis.[11] It remains unknown how T-cell activation induced by ICIs reduces the risk of infection.

Randomised clinical trials and meta-analyses involving temsirolimus and everolimus in patients with renal cell carcinoma have shown an approximately 2-fold increase in the risk of all grade of infection and an approximately 2.6-fold increase in high-grade infections compared with the control arm.[12 13] While the adverse event (AE) risks, including infection, of each anticancer agent in patients with certain cancer types have been evaluated, common AEs according to class of anticancer agents have not been fully evaluated. Here, we retrospectively estimated the infection risk in patients with cancer treated with investigational agents in phase I studies.

PATIENTS AND METHODS

A total of 76 phase I trials with malignant solid tumours were performed at the National Cancer Centre Hospital in Japan between January 2007 and January 2017. After the exclusion of combination phase I trials, 641 consecutive patients with malignant solid tumours were enrolled in a cumulative total of 803 trials and received the investigational agents at the assigned dose and administration. Because 112 patients were enrolled in multiple trials, clinical information from the first phase I trial in which each patient received investigational agents was analysed in this retrospective study. Eligibility criteria in almost all phase I trials were age ≥20 years, Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–2, adequate major organ function, refractory to standard treatment and recovery from all previous treatments. Exclusion criteria in almost all phase I trials were serious concomitant disorders, including active infection, severe heart disease and uncontrolled diabetes; interstitial pneumonia or pulmonary fibrosis; primary central nervous system tumours or symptomatic central nervous system metastases. Patient characteristics, treatment regimen, AEs, clinical outcomes and laboratory data were collected from the electronic medical chart which our hospital introduced in January 2007. All patients provided informed consent for enrolment in the phase I trials and for the comprehensive use of clinical data for research purposes.

Infection-related AEs and their assessment

Infection-related data consisted of events with infection-related symptoms according to the discretion of the treating physician. Every infection-related AE was recorded if the patient experienced it during treatment or within 30 days after trial termination. After reviewing the medical chart associated with the clinical report form, we re-evaluated infection-related AEs in terms of the causal relationship between investigational agents and the infection-related AE and its grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0.[14] Grade 1 (mild) oral mucositis was excluded from infection-related AEs because we could not distinguish clearly between infection and other mucous membrane disorders.

Statistical analysis

The investigational agents were classified into four groups: CTA, PAM, MTA (except PAM inhibitor) and ICI. Treatment duration was defined as the date of the initiation of the phase I trial to the termination of treatment due to progressive disease, ≥grade 3 AEs, patient withdrawal or death. Treatment durations with and without infection-related AEs were compared by Mann-Whitney U test. ORs of infection-related AEs during treatment with CTA, PAM and ICI were calculated and compared with the ORs of MTA which were used to treat the largest numbers of patients and were considered to confer a relatively low infection risk.

Monitoring for time to onset of an infection-related AE analysis started at the date of initiation of the phase I trial and ended on the date of the first occurrence of an infection-related AE, 30 days after study termination, death or 31 August 2018, whichever came first. We estimated the time-to-event curves using the Kaplan-Meier method as the censoring if the date of 30 days after termination, death or 31 August 2018 occurred. Cox regression

test was used to compare the risk according to groups. All p values were two-sided. All the statistical analyses were performed using GraphPad Prism V.8.0 (GraphPad Software).

RESULTS

Between January 2007 and January 2017, 641 patients entered 72 phase I trials (table 1). Median age was 58 years (range 18–83); 318 (49.7%) were female. Although patients with ECOG-PS 2 could participate in some phase I trials, almost all patients were ECOG-PS 0–1. The predominant cancer type in the 641 patients was gastrointestinal tumour (n=136, 21.2%), hepato-pancreatico-biliary tumour (n=113, 17.6%), sarcoma (n=109, 17.0%), lung tumour (n=102, 15.9%), breast tumour (n=53, 8.3%) and gynaecological tumour (n=42, 6.6%). A total of 35 patients were treated with CTAs (5.5%), 61 with PAMs (9.5%), 445 with MTAs (69.4%) and 100 with ICIs (15.6%). Patient characteristics, including the existence of a primary lesion, brain metastasis, lung complications, diabetes mellitus, ECOG-PS, the reason for termination and cancer type were not necessarily balanced among the four groups.

Infection-related AEs

Among the 641 patients, 132 (20.6%) patients experienced one or more infection-related AEs (table 2). Table 3 shows the occurrence of infection-related AEs and treatment duration by groups of investigational agents. The median treatment duration did not significantly differ between patients with any grade of infection-related AEs and in patients without infection-related AEs (p=0.09, Mann-Whitney U test). In the CTA group, 31.4% of patients experienced infection-related AEs, and the median treatment duration was 21 days with any grade of infection-related AEs and 38.5 days without (p=0.07). In the PAM group, 42.6% of patients experienced infection-related AEs, showing a significant difference in median treatment duration of 98 days with any grade of infection-related AEs and 32 days without (p=0.004). Among PAM group, the incidences of any grade and grade ≥3 infection-related AEs with PI3K or AKT inhibitors were similar to those in patients administered mTOR inhibitors (any grade, 0.364 vs 0.441; grade ≥3, 0.087 vs 0.088, respectively), although the incidence with dual PI3K/mTOR inhibitors was obviously high (0.75 and 0.50, respectively). In the MTA group, 17.3% of patients experienced infection-related AEs, and the median treatment duration was 56 days with any grade of infection-related AEs and 44 days without (p=0.36). In the ICI group, 18.0% of patients experienced infection-related AEs, with a median treatment duration of 200 days with any grade of infection-related AEs vs 84 days without (p=0.04). The ORs compared with MTAs were 2.19 (95% CI 1.03 to 4.66; p=0.04) for CTAs, 3.55 (95% CI 2.02 to 6.24; p<0.001) for PAMs and 1.05 (95% CI 0.60 to 1.85; p=0.87) for ICIs, respectively.

Forty-six (7.2%) patients developed 50 grade ≥3 infection-related AEs, including febrile neutropenia (n=13), lung infection (n=13), biliary tract infection (n=9), colitis (n=4) and oral mucosal infection (n=3) (table 4). One patient with biliary tract infection died. Patients treated with CTAs and PAMs with grade ≥3 infection-related AEs had a shorter treatment duration than those without. The ORs compared with MTAs were 4.78 (95% CI 1.98 to 11.5; p<0.001) for CTAs, 2.09 (95% CI 0.87 to 5.04; p=0.10) for PAMs and 0.85 (95% CI 0.32 to 2.27; p=0.74) for ICIs, respectively.

Results for patient characteristics, treatment duration and OR are shown in online supplementary tables 1 and 2 for infection-related AEs as all events with infection-related symptoms without excluding grade 1 (mild) oral mucositis. Similar results were obtained from the analyses including and excluding grade 1 oral mucositis.

Time to the first infection-related AE

At the data cut-off of 31 August 2018, the median follow-up time was 312 days (range 13–2750 days). A total of 524 patients died and 117 were censored. Among 47 living patients of the 117 censored, 11 patients remained on treatment. The reasons for the termination of a phase I trial were AE (n=81), progressive disease (n=542), patient's withdrawal (n=4), sponsor's decision (n=2) and treatment-related death (n=1).

The time to the first infection-related AE using the Kaplan-Meier method is shown in figure 1. The risks of any infection-related AE for the CTA group were not significantly higher than those for MTA (HR 1.84 (95% CI 0.82 to 4.11); p value=0.05 and significantly higher for PAM 3.96 (95% CI 2.18 to 7.22); p value<0.001). Meanwhile, the risk for any infection-related AE for ICI was not significantly different from that for MTA (HR 0.71 (95% CI 0.464 to 1.10); p=0.19).

DISCUSSION

Our retrospective study examined infection risk in patients treated with investigational agents in a phase I study. It has already been reported that in phase I studies that the incidence of all grade and grade ≥3 infection in single-agent PAMs is significantly higher than that in MTAs (OR 4.26 (95% CI 1.9 to 9.1); 3.74 (95% CI 1.1 to 12.4), respectively). Furthermore, dual PI3K/mTOR inhibitors were associated with a significantly higher risk of infection compared with PI3K, AKT or mTOR inhibitors alone.[15] Those results demonstrated that the infection risk with PAMs is high in patients with a variety of malignant solid tumours who entered phase I studies as well as in those with renal cell carcinoma as previously reported in randomised studies.[12 13] Our results validate this. Our study presented that the treatment duration, possibly affecting the incidence rate due to lead-time bias in patients with infection-related AEs, was different in some investigational agents from that without infection-related AEs.

Table 1 Patient characteristics according to classification of investigational agents

	CTA	PAM	MTA	ICI	Total
Number of patients (%)	n=35 (5.5%)	n=61 (9.5%)	n=445 (69.4%)	n=100 (15.6%)	n=641
M/F	24 (68.6)/11 (31.4)	20 (32.8)/41 (67.2)	224 (50.3)/221 (49.7)	54 (54.0)/46 (46.0)	323 (50.3)/318 (49.7)
Age (median (range))	60 (36–71)	58 (26–77)	58 (18–83)	59 (34–76)	58 (18–83)
Height (median (range))	164.0 (141.3–175.0)	158.0 (148.2–182.8)	162.0 (141.2–186.4)	162.7 (142.0 to 181.2)	162.2 (141.2–186.4)
Body weight (median (range))	58.7 (41.4–81.8)	55.9 (36.0–97.0)	57.4 (31.5–92.9)	59.0 (40 to 101.7)	57.4 (31.5–101.7)
BMI (median (range))	22.5 (17.8–28.4)	21.8 (15.3–32.0)	21.7 (14.1–34.8)	22.2 (14.6 to 35.5)	21.9 (14.1–35.5)
BSA (median (range))	1.62 (1.30–1.93)	1.56 (1.25–2.12)	1.60 (1.17–2.09)	1.62 (1.29 to 2.15)	1.60 (1.17–2.15)
Primary lesion (+)	15 (42.9)	12 (19.7)	138 (31.0)	45 (45.0)	210 (32.8)
Brain metastasis (+)	1 (2.9)	4 (6.6)	29 (6.5)	8 (8.0)	42 (6.6)
Lung complication (+)	1 (2.9)	1 (1.6)	23 (5.2)	3 (3.0)	28 (4.4)
Diabetes mellitus (+)	6 (17.1)	1 (1.6)	36 (8.1)	14 (14.0)	57 (8.9)
ECOG-PS 0/1/2	14 (40.0)/21 (60.0)/0 (0.0)	35 (57.4)/25 (41.0)/1 (1.6)	203 (45.6)/242 (54.4)/1 (0.002)	40 (40.0)/60 (60.0)/0 (0.0)	291 (45.4)/348 (54.2)/2 (0.3)
Reason for termination					
Progressive disease	22 (62.9)	45 (73.8)	389 (87.4)	86 (86.0)	542 (84.6)
Adverse event	12 (34.3)	15 (24.6)	44 (9.9)	10 (10.0)	81 (12.6)
Ongoing	0 (0.0)	0 (0.0)	7 (1.6)	4 (4.0)	11 (1.7)
Other reason	1 (2.8)	1 (1.6)	5 (1.1)	0 (0.0)	7 (1.1)
Cancer type					
Gastrointestinal tumour	12 (34.3)	5 (8.2)	103 (23.1)	16 (16.0)	136 (21.2)
HPB tumour	3 (8.6)	10 (16.4)	82 (18.4)	18 (18.0)	113 (17.6)
Sarcoma	2 (5.7)	16 (26.2)	91 (20.4)	0 (0.0)	109 (17.0)
Lung tumour	11 (31.4)	6 (9.8)	61 (13.7)	24 (24.0)	102 (15.9)
Breast tumour	1 (2.9)	12 (19.7)	39 (8.8)	1 (1.0)	53 (8.2)
Gynaecological tumour	3 (8.6)	9 (14.8)	22 (4.9)	8 (8.0)	42 (6.6)
Melanoma	0 (0.0)	0 (0.0)	13 (2.9)	9 (9.0)	22 (3.4)
Thymic tumour	1 (2.9)	0 (0.0)	13 (2.9)	7 (7.0)	21 (3.3)
CUP	0 (0.0)	1 (1.6)	7 (1.6)	4 (4.0)	12 (1.9)
Head and neck tumour	2 (5.7)	1 (1.6)	3 (0.01)	5 (5.0)	11 (1.7)
Mesothelioma	0 (0.0)	0 (0.0)	5 (0.01)	5 (5.0)	10 (1.6)
Urological tumour	0 (0.0)	1 (1.6)	4 (0.01)	2 (2.0)	7 (1.1)
Others	0 (0.0)	0 (0.0)	2 (0.004)	1 (1.0)	3 (0.5)

*Other reason: patient's withdrawal, sponsor's decision, treatment-related death.
BMI, body mass index; BSA, body surface area; CTA, cytotoxic agent; CUP, carcinoma of unknown primary; ECOG-PS, Eastern Cooperative Oncology Group performance status; HPB, hepato-pancreatico-biliary tumour; ICI, immune checkpoint inhibitor; MTA, molecular targeted agent; PAM, PI3K-AKT-mTOR.

Table 2 Patients' characteristics and type of the investigational drugs with infection-related adverse event or without

	Total	Infection (–)	Infection (+)	Grade ≥3 infection (–)	Grade ≥3 infection (+)
Number	641	509 (79.4%)	132 (20.6%)	595 (92.8%)	46 (7.2%)
M/F	323 (50.3)/318 (49.7)	258/251	65/67	293/302	30/16
Age	58 (18–83)	58 (18–77)	59.5 (21–83)	58 (18–77)	61 (21–83)
Height	162.2 (141.2–186.4)	162.2 (141.3–186.4)	162.3 (141.2–183.2)	161.8 (141.2–186.4)	164.0 (148.6–176)
Body weight	57.4 (31.5–101.7)	57.5 (31.5–101.7)	57.4 (34.7–97)	57.5 (31.5–101.7)	55.7 (36–80)
BMI (median (range))	21.9 (14.1–35.5)	21.9 (14.1–35.5)	21.8 (14.4–32.0)	21.8 (14.1–35.5)	21.9 (15.9–28.0)
BSA (median (range))	1.60 (1.17–2.15)	1.60 (1.17–2.15)	1.60 (1.25–2.12)	1.60 (1.17–2.15)	1.57 (1.25–1.94)
Primary lesion +	210 (32.8)	174 (34.2)	36 (27.3)	198 (33.3)	12 (26.1)
Brain metastasis +	42 (6.6)	29 (5.7)	13 (9.8)	37 (6.2)	5 (10.9)
Lung complication +	28 (4.4)	20 (3.9)	8 (6.1)	25 (4.2)	3 (6.5)
Diabetes mellitus +	57 (8.9)	46 (9.0)	11 (8.3)	52 (8.7)	5 (10.9)
PS 0/1/2	291/348/2	243/265/1	48/83/1	277/317/1	14/31/1
Type of investigational agent					
CTA	35	24	11	27	8
PAM	61	35	26	54	7
PI3K/AKT/mTOR/Dual	21/2/34/4	14/1/19/1	7/1/15/3	19/2/31/2	2/0/3/2
MTA	445	368	77	419	26
Small molecule/antibody/ADC/Other	342/68/23/12	278/63/15/12	64/5/8/0	320/66/21/12	22/2/2/0
ICI	100	82	18	95	5
Cancer type					
Gastrointestinal tumour	136	111	25	124	12
HPB tumour	113	90	23	104	9
Sarcoma	109	80	29	101	8
Lung tumour	102	87	15	97	5
Breast tumour	53	40	13	47	6
Gynaecological tumour	42	35	7	41	1
Melanoma	22	18	4	22	0
Thymic tumour	21	18	3	21	0
CUP	12	9	3	10	2
Head and neck tumour	11	9	2	10	1
Mesothelioma	10	7	3	9	1
Urological tumour	7	3	4	6	1
Other	3	2	1	3	0

CTA, cytotoxic agent; CUP, carcinoma of unknown primary; HPB, hepato-pancreatico-biliary tumour; ICI, immune checkpoint inhibitor; MTA, molecular targeted agent; PAM, PI3K-AKT-mTOR.

Table 3 Treatment duration and OR according to classifications of the investigational agents

Treatment duration, days	Total	Infection (–)	Infection (+)	Grade ≥3 infection (–)	Grade ≥3 infection (+)
Overall	n=641	n=509	n=132	n=595	n=46
Mean (SD)	120.4 (194.5)	109.1 (170.9)	163.8 (263.1)	124.1 (198.9)	72 (115.1)
Median (IQR)	54 (29–126)	50 (29–121)	63.5 (30.8–173)	57 (29–128)	34 (21–68)
Range	4–1659	4–1659	4–1547	4–1659	4–686
P value		0.09		<0.001	
CTA	n=35	n=24	n=11	n=27	n=8
Mean (SD)	53.8 (50.9)	65.5 (56.3)	28.4 (22.2)	63.1 (54.6)	22.5 (9.20)
Median (IQR)	22 (21–84.5)	38.5 (21–121)	21 (20.5–26.5)	38 (21–106)	21 (20–24.3)
Range	8–171	9–171	8–91	9–171	8–39
P value		0.07		0.08	
PAM	n=61	n=35	n=26	n=54	n=7
Mean (SD)	98.2 (108.7)	73.6 (82.7)	131.2 (130.7)	102.1 (113.3)	68.1 (59.8)
Median (IQR)	62 (30–121)	32 (30–87.5)	98 (49–170.8)	62.5 (30.3–121)	41 (27.5–98)
Range	9–665	15–398	9–665	15–665	9–176
P value		0.004		0.49	
MTA	n=445	n=368	n=77	n=419	n=26
Mean (SD)	114.2 (182.2)	107.1 (167.6)	148.1 (238.5)	116.3 (184.4)	81.5 (141.0)
Median (IQR)	46 (28–122)	44 (28–119.5)	56 (30–131)	50 (28.5–128)	34.5 (21.3–67)
Range	4–1536	4–1339	4–1536	4–1536	4–686
P value		0.36		0.04	
ICI	n=100	n=82	n=18	n=95	n=5
Mean (SD)	184.5 (285.5)	145.9 (222.8)	360.3 (445.2)	188.5 (291.5)	107.2 (110.7)
Median (IQR)	84.5 (44–196)	84 (43.3–153.8)	200 (56.5–371.5)	85 (44.5–201)	56 (36–119)
Range	9–1659	9–1659	30–1547	9–1659	30–295
P value		0.04		0.62	
Positive rate			0.206		0.072
CTA			0.314		0.229
PAM			0.426		0.115
MTA			0.173		0.058
ICI			0.180		0.050
OR					
CTA vs MTA		2.19 (1.03–4.66), p=0.04		4.78 (1.98–11.5), p<0.001	
PAM vs MTA		3.55 (2.02–6.24), p<0.001		2.09 (0.87–5.04), p=0.10	
ICI vs MTA		1.05 (0.60–1.85), p=0.87		0.85 (0.32–2.27), p=0.74	

Treatment duration with infection-related adverse events and without were compared by Mann-Whitney U test.
CTA, cytotoxic agent; ICI, immune checkpoint inhibitor; MTA, molecular targeted agent; PAM, PI3K-AKT-mTOR.

In randomised phase III trials in which the primary end point is generally efficacy, we can evaluate only the incidence rate and OR of toxicity. Here, we estimated the time-to-event curves using the Kaplan-Meier method and analysed the risk according to groups by Cox regression test. Our time to event analysis based on individual data demonstrated the risks for any infection-related AEs with CTAs were not significantly different from those with MTAs (HR 1.84 (95% CI 0.820 to 4.11); p=0.05 and with PAMs significantly different 3.96 (95% CI 2.18 to 7.22); p<0.001).

Several PAMs have already been approved for the treatment of specific types of cancers, such as chronic lymphocytic leukaemia, malignant lymphoma, renal cell cancer and neuroendocrine tumours. Recently, in a randomised phase III trial, alpelisib, an α-specific PI3K inhibitor, plus fulvestrant demonstrated prolonged progression-free survival among patients with *PIK3CA*-mutated, hormone

Table 4 Severe infection-related adverse events

	Number of events (n=50)
Febrile neutropenia	13
Lung infection	13
Bile tract infection	9
Colitis	4
Peritonitis	2
Oral mucositis	3
Liver abscess	2
Cellulitis	2
Urinary tract infection	1
Sepsis	1

receptor-positive, HER2-negative advanced breast cancer who had previously received endocrine therapy compared with placebo plus fulvestrant.[16] Alpelisib in combination with olaparib also induced a noteworthy preliminary clinical response in epithelial ovarian cancer.[17] In the future, treatment opportunities for PAMs may increase for the treatment of a variety of malignant tumours harbouring PAM pathway alterations. We suggest that intense infection control and prevention might be required in the treatment with PAMs, especially in the use of dual inhibitors.

In the escape phase based on the theory of cancer immunoediting, ICI can enhance T-cell function by releasing immune suppression systems, resulting in antitumour activity.[18 19] However, the nature of the enhanced T-cell function is not for innate immunity against foreign substances, but for adaptive immunity. In our study, the time to event analysis in ICI demonstrated that the infection risk was not significantly different from that in MTA (HR 0.71 (95% CI 0.464 to 1.10); p=0.19). In addition, the ORs of any grade, and grade ≥3 infection-related AEs with ICIs were similar to those with MTAs (OR 1.05 (95% CI 0.60 to 1.85); p=0.87; 0.85 (95% CI 0.32 to 2.27); p=0.74, respectively). Therefore, we do not consider that ICIs confer a lower infection risk in patients with solid tumours than MTAs. Some case reports have reported the acute exacerbation of underlying infection, such as pulmonary tuberculosis, during anti-PD-1 antibody therapy.[20–22] Retrospective studies also demonstrated increased risk of infection in patients receiving ICIs along with immunosuppressive agents, including corticosteroids and infliximab, as well as in patients with concomitant diabetes mellitus.[23 24] However, because the subjects with underlying infection, uncontrolled diabetes mellitus or the concomitant use of immunosuppressive agents were excluded based on the exclusion criteria of each phase I study, these events were not recorded in our study.

In our study, treatment duration by groups of investigational agents differed substantially among PAM, CTA and MTA patients with and without infection-related adverse events, because the reasons for the termination of phase I trials were quite different. Most patients who received PAMs, MTAs and ICIs terminated their phase I trial due to disease progression. In contrast, most patients who received CTAs were removed from the trial due to AEs as well as disease progression. Therefore, we concluded that patients with infection-related AEs who received CTAs tended to have a shorter treatment duration than those without.

Several limitations of this study warrant mention. First, the primary end point in each phase I study was not infection risk but rather the maximum tolerated dose and recommended phase II dose. During the phase I studies, the detailed information on AEs, including infection, was assessed continuously based on CTC-AE grade and

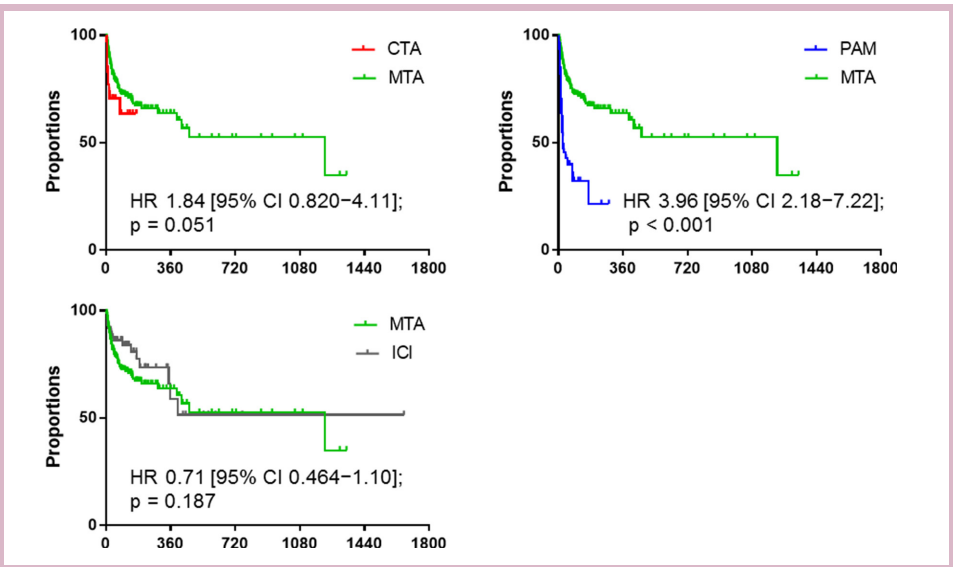

Figure 1 Time to first infection-related adverse event compared with a molecular targeted agent. CTA, cytotoxic agent; MTA, molecular targeted agent; PAM, phosphatidylinositol 3 kinase/Akt/mammalian target of rapamycin.

causal relationship. Therefore, we think the assessment of infection-related AEs in our study was reliable. Second, we included a variety of subjects with malignant solid tumours refractory to standard treatment, intolerant of standard treatment or for whom no standard therapy exists. Certainly, the dose, detailed target and the treatment duration of anticancer agents were all different. Patient characteristics were not necessarily balanced among the four groups, because the global trends in the distribution of cancer types and the groups of investigational agents in phase I trials have changed over the past decades.[25] Third, we did not define patients with cancer who were not under treatment or healthy persons as controls, but rather patients treated with MTAs. We consider that our results can be extrapolated to patients with malignant solid tumours undergoing chemotherapy.

In conclusion, our results validated that PAMs and CTAs conferred a higher infection risk in patients with malignant solid tumours compared with MTAs in both the time to event analysis as well as the OR. We suggest that ICIs have a similar infection risk to that of MTAs.

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