

Increased frequency of acute reactions to iodinated contrast media in cancer patients treated with anti-CTLA-4 immunomodulatory antibodies

Laura Ridolfi^{a,*}, Francesco De Rosa^a, Elisabetta Petracci^b, Giorgia Gentili^b, Oriana Nanni^b, Alberto Farolfi^c, Carla Casadei^d, Alice Rossi^e, Nicola Gentili^f, Massimo Guidoboni^a

^a Immunotherapy and Cell Therapy Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

^b Unit of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

^c Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

^d Anesthesiology Service, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

^e Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

^f IT Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

ABSTRACT

Contrast-enhanced computed tomography (CECT) is an indispensable tool in the management of cancer patients. However, this procedure can be complicated by the development of acute adverse reactions (ARs) to iodinated contrast media (ICM). On the basis of the hypothesis that cancer immunotherapy, in particular with immune checkpoint inhibitors, increases the incidence of allergic-like immediate ARs to ICM with respect to “standard” cancer chemotherapy/targeted therapy (CHT) we retrospectively evaluated the incidence of CECT-related immediate ARs in cancer patients undergoing cancer treatments. All patients who underwent at least one CECT scan after starting any cancer treatment between 2006 and 2014 were included in a mono-institutional radiological database. The staff of the Radiology Unit recorded any ARs that occurred within 30 min of the ICM injection and classified them as “allergic-like” or “physiologic” and graded as mild, moderate, or severe according to the American College of Radiology (ACR) Manual on Contrast Media, version 10.1. Fifty-nine of the 3,521 patients included in the database received ipilimumab (Ipi), 75 received cytokines (Cys), and the remaining 3,387 received non-immunologic agents (CHT). Overall, 71 (2%) patients suffered ICM-related ARs. The incidence of ICM-related ARs was higher in Ipi- and Cy-treated patients than in those who received CHT (12%, 5%, and 2%, respectively). Our data show that immunological cancer treatments, particularly Ipi, considerably increase the proportion of patients suffering CECT-related immediate ARs with respect to non-immunologic agents. Although these findings need to be validated in larger prospective studies, they serve as a “wake-up call” for radiologists to closely monitor patients who have previously received cancer immunotherapy with anti-cytotoxic T-lymphocyte antigen-4 antibodies when using ICM in order to reduce the risk of potentially severe immediate ARs.

Introduction

Contrast-enhanced computed tomography (CECT), an indispensable tool in the management of cancer patients to evaluate the response to treatment, can be complicated by the development of acute adverse reactions (ARs) to iodinated contrast media (ICM) [1], however low-osmolar contrast media has reduced the incidence of acute ICM-related ARs to 0.2–0.7% [2–4]. The American College of Radiology (ACR) classifies ICM-related ARs as allergic-like (e.g., urticaria, erythema, and bronchospasm) and physiologic (e.g., nausea, vomiting, and hypertension) reactions [5]. Allergic-like reactions are probably independent of the dose and concentration and induced by alteration of the immune system balance. Conversely, physiologic reactions are frequently dose and concentration-dependent [6,7].

The immune system protects the host from exogenous pathogens by distinguishing “self” from “non-self” using stimulatory and inhibitory

components. The cell surface molecule cytotoxic T-lymphocyte antigen 4 (CTLA-4) limits the body's response to autoantigens, helps to diversify the T-cell populations, and limits the severity of autoimmunity [8]. Ipilimumab (Ipi), a humanized immunoglobulin G1 monoclonal antibody that recognizes and blocks CTLA-4, is approved for the treatment of metastatic melanoma [9].

Hypothesis

Ipi is associated with adverse events resulting from drug-induced weakening of self-tolerance mechanisms and consequent autoimmune toxicity [10]. CTLA-4 blockade also emphasize the humoral response to allergens and may increase hypersensitivity reactions [11] like the ICM-related allergic-like ones. On the basis of a previous study [12] we designed a retrospective study to evaluate the occurrence of immediate reactions to ICM used for CECT in cancer patients treated with CTLA-4-

* Corresponding author at: IRST IRCCS, Via Maroncelli 40, 47014 Meldola, FC, Italy.

E-mail address: laura.ridolfi@irst.emr.it (L. Ridolfi).

blocking antibodies and other therapies. We collected information on all CECT-related ARs from 2006 to 2014 in patients treated with Ipi, cytokines (Cys), or chemotherapy/targeted therapy (CHT).

Materials and methods: evaluation of the hypothesis

Using an institutional radiological database, we identified all consecutive cancer patients who underwent at least one CECT scan after starting any medical cancer treatment at our institute between January 1, 2006, and December 31, 2014. All were outpatients with a performance status of 0–1 on the Eastern Cooperative Oncology Group scale. The following data were extracted for each patient: personal ID (tax code), gender, date of birth, date of CT scans, type of ICM injected, and the number of CECT scans performed in the 2 years prior to the first index CECT scan. The index CECT scan was defined as the first CECT scan performed after the first treatment cycle during the time period considered. All CT scans were performed using a 256-slice CT scanner. The low-osmolar ICM employed at our institution during the study period was predominantly (80%) iomeprol [12,13].

The staff of the Radiology Unit recorded any ARs that occurred within 30 min of the ICM injection and classified them as “allergic-like” or “physiologic” and graded as mild, moderate, or severe according to the ACR Manual on Contrast Media, version 10.1. We used the patient’s tax code to link the clinical database to the radiological database.

Descriptive statistics were reported as frequencies and percentages for categorical variables and as means $\pm$ standard deviation for continuous variables. For each therapeutic regimen, the frequency of patients who experienced CECT-related ARs was computed. The association between categorical variables was assessed by the Pearson’s Chi-squared test or the Fisher’s exact test. The association between continuous variables was assessed by the Student’s *t*-test or the *F*-test. A two-sided *P* value < 0.05 was deemed statistically significant in all analyses. The Bonferroni correction was used for the ANOVA post-hoc comparison. All statistical analyses were carried out using STATA 10.1 statistical software.

Results

The final database included 3,521 patients who underwent first- or second-line systemic treatment for metastatic disease and were re-evaluated by CECT at the end of treatment (Fig. 1). Of these, 59 received Ipi, 75 received Cys (low-dose interferon- α and/or interleukin-2), and the remaining 3,387 received CHT. Patient Characteristics are reported in Table 1.

The mean number of CT scans performed before the index CT scan did not significantly differ between the groups ($p = 0.190$). Seventy-one (2.01%) patients in the whole series exhibited acute ICM-related ARs during the study period. The median number of days elapsed between the end of treatment and the CT scan during which ARs were noted was 83 (range 8–898 days) in the Ipi group, 14.5 (range 2–333 days) in the Cy group, and 22 (range 2–962 days) in the CHT group. The incidence of ARs significantly ($p < 0.001$) differed between the treatment groups; the percentage of patients who experienced mild-

to-severe ICM-related ARs was 12% in the Ipi group (7/59), 5% in the Cy group (4/75), and 2% in the CHT group (60/3,387) (Table 2). Of the 59 patients treated with Ipi, 13 (22%) had previously received Cy-containing therapy. No patient who received Cys had previously been treated with Ipi, and no patient who received CHT had previously been treated with Cys or Ipi.

All the ARs observed in the Ipi and Cy groups were of the allergic-like type, while 10% of the ARs observed in the CHT group were of the physiologic type (6/60) (Table 3). All seven Ipi-treated patients who experienced ICM-related ARs had advanced melanoma, with more than one site of metastasis and none of these patients had known allergies to other substances or drugs. Two patients experienced a severe reaction to the ICM, two experienced a moderate reaction, and three experienced a mild reaction. The percentage of melanoma patients who experienced ICM-related ARs was significantly higher among those treated with Ipi than among those who received other therapies (7/48 vs. 3/133, $p = 0.004$). This excludes the possibility that melanoma patients had a higher risk of suffering ICM-related ARs.

Discussion

The introduction of Ipi into clinical practice has dramatically changed the natural history of advanced melanoma [9–14]. The effects of CTLA-4 blockade include increased production of “allergic” Cys and increased level of immunoglobulin E. Given that allergic-like reactions to ICM are partially immune-mediated, we wondered if they might be intensified by cancer treatments that alter the immune system balance. We thus decided to retrospectively investigate whether patients previously treated with Ipi had a higher incidence of allergic-like reactions to ICM than those who received other treatments. Our findings strongly support this hypothesis. In fact, patients treated with Ipi had a 5-fold higher risk of suffering immediate ARs to ICM than patients who received CHT. Moreover, all reactions observed in Ipi patients were of the allergic-like type. Patients treated with Cy-containing regimens also had an increased risk of suffering ARs, albeit lower than that observed for Ipi-treated patients, which lends further weight to the theory that immunological mechanisms are involved in the pathogenesis of immediate reactions to ICM.

Conclusions

Our findings need to be validated in a larger population but they alert oncologists about “new” Ipi-induced irAEs and forewarn radiologists of the need to carefully monitor patients who have been previously treated with anti-CTLA-4 antibodies when using ICM. Given the rapid clinical development of new immunomodulatory antibodies to treat a wide range of tumors, our study also highlights the need for further investigations aimed at addressing ARs in patients with different types of tumors.

Funding

This research received no specific grant from any funding agency in

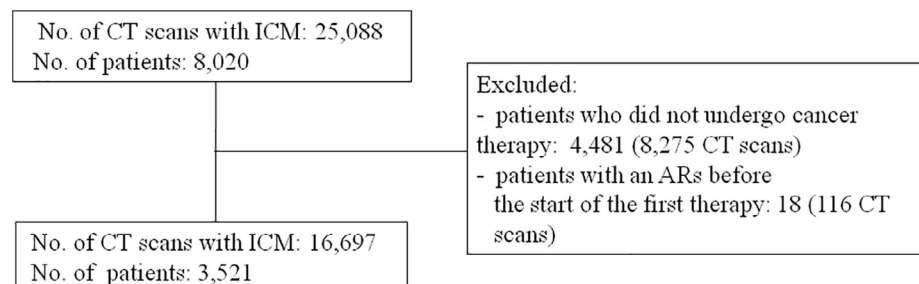


Fig. 1. The number of CECT scans performed was extracted from the database and refers to cancer patients who underwent at least one CECT scan and who completed at least one cycle of therapy between January, 2006, and December, 2014. Only patients receiving first- or second-line treatment for advanced disease were included in the database.

Table 1
Patient Characteristics According to the Therapy Group.

	Therapy groups			All No. = 3,521	P value
	Ipi No. = 59	Cys No. = 75	CHT No. = 3,387		
<i>Gender, No. (%)</i>					
Female	18 (30.5)	31 (41.3)	1,644 (48.5)	1,693 (48.1)	0.011
Male	41 (69.5)	44 (58.7)	1,743 (51.5)	1,828 (51.9)	
Mean age in years at start of therapy $\pm$ SD	59.8 $\pm$ 12.3	57.3 $\pm$ 13.0	63.8 $\pm$ 12.7	65.6 $\pm$ 12.7	< 0.001
<i>Type of diagnosis, No. (%)</i>					
Melanoma	48 (81.4)	59 (78.7)	74 (2.2)	181 (5.1)	< 0.001
Hematologic tumors	0 (0.0)	1 (1.3)	439 (13.0)	440 (12.5)	
Solid tumors	11 (18.6)	15 (20.0)	2,874 (84.8)	2,900 (82.4)	

CHT = chemotherapy/targeted therapy, Cys = cytokines, Ipi = ipilimumab, SD = standard deviation.

Table 2
ARs to Treatment.

	Patients who suffered an AR (No. = 71) No. (%)	Patients who did not suffer an AR (No. = 3,450) No. (%)	P value	Number of CECT scans performed before the AR Mean $\pm$ SD [minimum–maximum]
<i>Gender, No. (%)</i>				
Female	36 (50.7)	1,657 (48.0)	0.655	
Male	35 (49.3)	1,793 (52.0)		
Mean age in years at start of therapy $\pm$ SD	59.0 $\pm$ 1.3	63.7 $\pm$ 0.22	0.002	
<i>Treatment groups, No. (%)</i>				
Ipi (No. = 59)	7 (11.8%)	52 (88.1%)	< 0.001	6.4 $\pm$ 4.5 [1–13]
Cys (No. = 75)	4 (5.3%)	71 (94.7%)		4.3 $\pm$ 2.2 [1–6]
CHT (No. = 3,387)	60 (1.8%)	3,327 (98.2%)		4.1 $\pm$ 3.1 [1–15]
<i>Diagnosis, No. (%)</i>				
Melanoma	10 (14.1)	171 (5.0)	< 0.001	
Hematologic tumors	2 (2.8)	438 (12.7)		
Solid tumors	59 (83.1)	2,841 (82.3)		

AR = adverse reaction, CECT = contrast-enhanced computed tomography, CHT = chemotherapy/targeted therapy, Cys = cytokines, Ipi = ipilimumab, SD = standard deviation.

Table 3
Classification of CECT-related ARs According to the American College of Radiology Manual on Contrast Media.*

	Allergic-like			Physiologic		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Ipi (N = 7)	3	2	2	0	0	0
Cys (N = 4)	2	2	0	0	0	0
CNT (N = 60)	45	8	1	5	1	0

AR = adverse reaction, CECT = contrast-enhanced computed tomography, CHT = chemotherapy/targeted therapy, Cys = cytokines, Ipi = ipilimumab.

* Version 10.1.

the public, commercial, or non-for-profit sectors.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.mehy.2018.07.030>.

References

- [1] Katayama H. Adverse reactions to contrast media. What are the risk factors? Invest Radiol 1990;25(Suppl 1):S16–7.
- [2] Cochran ST, Bomyea K. Trends in adverse events from iodinated contrast media. Acad Radiol 2002;9(Suppl 1):S65–8.
- [3] Mortelet KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. AJR Am J Roentgenol 2005;184(1):31–4.
- [4] Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. AJR Am J Roentgenol 2008;191(2):409–15.
- [5] ACR manual on contrast media. ACR manual on contrast media, version 10.1. Available at: http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast%20Manual/2015_Contrast_Media.pdf [accessed november 03, 2015].
- [6] Brockow K. Immediate and delayed reactions to radiocontrast media: is there an allergic mechanism? Immunol Allergy Clin North Am 2009;29(3):453–68.
- [7] Zhang X, Liu F, Chen X, Zhu X, Uetrecht J. Involvement of the immune system in idiosyncratic drug reactions. Drug Metab Pharmacokinet 2011;26(1):47–59.
- [8] Wolchok JD, Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist 2008;13(Suppl 4):2–9.
- [9] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711–23.
- [10] Bertrand A, Kostine M, Barnette T, Truchetet ME, Schaefferbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med 2015;4(13). 211-015-0455-8.
- [11] Maazi H, Shirinbak S, den Boef LE, Fallarino F, Volpi C, Nawijn MC, et al. Cytotoxic T lymphocyte antigen 4-immunoglobulin G is a potent adjuvant for experimental allergen immunotherapy. Clin Exp Immunol 2013;172(1):113–20.
- [12] Farolfi A, Della Luna C, Ragazzini A, Carretta E, Gentili N, Casadei C, et al. Taxanes as a risk factor for acute adverse reactions to iodinated contrast media in cancer patients. Oncologist 2014;19(8):823–8.
- [13] Farolfi A, Carretta E, Luna CD, Ragazzini A, Gentili N, Casadei C, et al. Does the time between CT scan and chemotherapy increase the risk of acute adverse reactions to iodinated contrast media in cancer patients? BMC Cancer 2014;31(14). 792-2407-14-792.
- [14] Homet Moreno B, Parisi G, Robert L, Ribas A. Anti-PD-1 therapy in melanoma. Semin Oncol 2015;42(3):466–73.