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To cite this article: Ingrid Böhm, John Morelli, Knud Nairz, Patricia Silva Hasembank Keller & Johannes T. Heverhagen (2017) Myths and misconceptions concerning contrast media-induced anaphylaxis: a narrative review, *Postgraduate Medicine*, 129:2, 259-266, DOI: 10.1080/00325481.2017.1282296

To link to this article: <http://dx.doi.org/10.1080/00325481.2017.1282296>



Accepted author version posted online: 13 Jan 2017.  
Published online: 25 Jan 2017.



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CLINICAL FEATURE  
REVIEW

## Myths and misconceptions concerning contrast media-induced anaphylaxis: a narrative review

Ingrid Böhm<sup>a,b\*</sup>, John Morelli<sup>c\*</sup>, Knud Nairz<sup>a\*</sup>, Patricia Silva Hasembank Keller<sup>a</sup> and Johannes T. Heverhagen<sup>a,b</sup>

<sup>a</sup>Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, University of Bern, Bern, Switzerland; <sup>b</sup>Radiology Laboratory, Department Clinical Research, University of Bern, Bern, Switzerland; <sup>c</sup>Department of Radiology, St. John's Medical Center, Tulsa, OK, USA

### ABSTRACT

Contrast-enhanced radiological examinations are an increasingly important diagnostic tool in modern medicine. All approved and available contrast media (iodinated and gadolinium-based) are safe compounds that are well-tolerated by most patients. However, a small percentage of patients exhibit contrast medium-induced adverse drug reactions that are dose-dependent and predictable (type A) or an even smaller cohort experience so-called type B (dose-independent, non-predictable). To increase patients' safety, recommendations/guidelines have been put forth in the literature and advice passed down informally by radiologists in practice to ensure contrast media safety. Through these, both reasonable suggestions as well as misinterpretations and myths (such as the misleading terms "allergy-like" reactions, and "iodine-allergy", the wrong assumption that the initial contact to a contrast medium could not induce an allergy, the estimation that an anti-allergy premedication could suppress all possible adverse reactions, and interleukin-2 as a risk/trigger for contrast medium adverse events) have arisen. Since the latter are not only unhelpful but also potentially reduce patients' safety, such myths and misconceptions are the focus of this review.

### ARTICLE HISTORY

Received 14 July 2016  
Accepted 11 January 2017

### KEYWORDS

Contrast media; allergy; allergy-like; recombinant interleukin 2 protein; drug hypersensitivity; premedication; drug safety

## 1. Introduction

More than 100 million estimated procedures using iodinated radio-contrast media and 30 million procedures with gadolinium-based contrast agents are performed worldwide every year [1–3].

All available contrast materials are well tolerated and safe. However, adverse events and hypersensitivity reactions do still occur in a small percentage of patients.

The ongoing trend of increasing contrast media (CM) usage requires close adherence to all recommendations concerning their use. Such recommendations have been made on the basis of clinical observations and studies. However, due to the wealth of long-term experience with CM, certain incorrect assumptions, misconceptions, and myths have found their way into clinical practice, the scientific literature, and even consensus recommendations. The following paper addresses some of the relevant myths and misconceptions regarding hypersensitivity reactions induced by iodinated CM and gadolinium-based contrast agents. Such errors and myths persist in the minds of generations of healthcare professionals and lead to inappropriate action and ultimately a decrease in the overall safety of CM. The goal of this paper is to improve knowledge regarding these myths and misconceptions in order to avoid such errors in future. The article highlights up-to-date literature concerning selected myths and misconceptions that are still prevalent in clinical practice or alluded to in guidelines

put forth by US (American College of Radiology (ACR) Manual on Contrast Media) or European (European Society of Urogenital Radiology (ESUR) Guidelines on Contrast Media) societies [4,5].

## 2. Myth 1: CM can induce only 'allergy-like reactions'

Even without proper diagnosis, CM hypersensitivity reactions are called 'allergy-like,' 'anaphylactoid,' or 'allergic-like' reactions [4–15]. The origin may relate to the long tradition of using iodinated compounds as CM in radiology. From 1953 until 1985, only ionic iodinated CM were available. These substances had a high osmolality of 1500 mOsm/kg like diatrizoate, for example, which was responsible for the high percentage of adverse events (up to 12.7%) [16]. Since most of these reactions clinically resembled allergic reactions of the immediate type (i.e. urticaria, shortness of breathing, tachycardia, etc.), but were not IgE mediated, they have been called 'allergy like.'

Currently, most radiological units/clinics have replaced ionic iodinated CM by non-ionic compounds of low or iso-osmolality. Nevertheless, although there is a body of evidence that CM can induce true allergy reactions [17–26], hypersensitivity reactions are still called 'allergy like' without any allergy-test procedure [15]. Since an inexact nomenclature/

classification inhibits both effective clinical prophylactic management programs, and scientific progress, we recommend the most prevalent classification of adverse drug reactions that differentiates between type A and type B reactions [27] (Figure 1). Type A reactions are predictable, common, and physiologic, that is, related to the pharmacologic properties of a drug. Type B reactions are allergy or hypersensitivity reactions meaning that the reactions are unpredictable, uncommon, and usually not related to the pharmacological properties of a drug. It has been estimated that greater than 80% of CM adverse drug reactions are type A reactions and less than 20% are type B [28]. The Coombs–Gell classification further subdivides type B reactions in at least four categories (Table 1). CM-induced type B (hypersensitivity) reactions fit into this classification as well. Type I or immediate CM allergic reactions (e.g. urticaria, tachycardia, asthma/difficulty to breath) are most common, followed by type IV (or so-called delayed) reactions [29–33]. On the basis of allergy testing, it has become evident that some of the immediate hypersensitivity reactions induced by iodinated CM are IgE mediated: iodinated CM-specific IgE has been found in patients with positive skin tests [17–26]. Currently, the percentage of IgE positive CM-hypersensitivity reactions is unknown. But it has been demonstrated that the more severe a reaction, the more likely an IgE-mediated mechanism is involved [19–21,34].

Delayed/non-immediate reactions have a much broader spectrum of clinical symptoms than immediate reactions: besides

nonspecific symptoms (e.g. headache, heat feeling, nausea/vomiting, skin redness), specific clinical features such as maculopapular exanthema, fixed drug eruption, drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens–Johnson syndrome or toxic epidermal necrosis fit into this category [7,35–41]. Delayed reactions are mediated by allergen-specific T cell clones. Demonstration of CD4+ and CD8+T cell infiltrates expressing activation markers (e.g. CD25, CD69, CLA, and HLA-DR) in both non-immediate CM-induced skin lesions, and positive skin test results by immunohistological analyses provide evidence for this assumption [42–44]. Considering these findings it is difficult to explain an ‘allergy-like’ mechanism for such conditions. Rarely, type II reactions have been reported: intravascular immune hemolysis after iomeprol [45] and acute severe thrombocytopenia after non-ionic low-osmolality iodinated CM [46]. CM-vasculitis (type III reaction) is extremely rare [47].

Consequently, it would be most accurate to call the reactions ‘hypersensitivity’ if an allergy work-up has not been performed, and either ‘allergic reactions’ or ‘nonallergic reactions’ (allergy-like reactions) based upon the allergy test result [48,49] (Figure 1).

Allergy testing provides the opportunity to identify/verify the culprit CM (including all kind of contrast materials: iodinated CM, gadolinium-based contrast agents, and microbubbles used as contrast agents in the context of ultrasound examinations), and to find alternate CM for CM-enhanced radiological procedures in the future [19,21–24,35,50–55]. Immediate CM-hypersensitivity reactions are tested by skin prick test, and intradermal testing, and subsequently read after 15–20 min. Skin prick test of CM is usually done with undiluted compounds. Since this diagnostic tool produces only in a very small percentage of patients positive results [19,24,35,50,51,53–55], it is possible to omit skin prick test of CM. A higher rate of positive results can be obtained by the intradermal test. Currently, this procedure is performed with different CM concentrations. While some clinicians use diluted CM test concentrations ( $10^{-3}$  up to  $10^{-1}$ ) only, other started with dilutions, and test also undiluted CM in cases with negative test results to the dilutions [19,44,50,51,53–56]. It is noteworthy that the lower the CM test concentration, the lower the percentage of positive reactions [19]. This means that some possibly existing reactions may remain unidentified by using diluted CM only. As a consequence, the negative predicting value of negative-tested CM runs in parallel to the used test concentration: the lower the concentration the lesser the negative predicting value. In other words, due to the low sensitivity, and high specificity the diagnostic value of the intradermal test with diluted CM is limited [56].

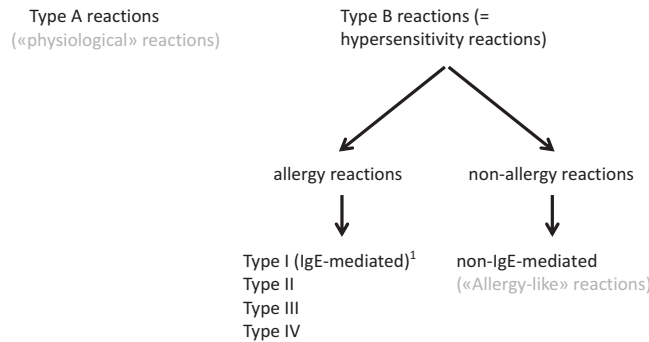


**Figure 1.** Schematic drawing showing the established classification of adverse drug reactions in general and of contrast medium reactions in particular in so-called type A (i.e. predictable, dose-dependent), and type B or hypersensitivity reactions (non-predictable, dose-independent) (according to [27]). Type B reactions can be further subdivided into non-allergy and allergy reactions. The latter manifest according to the Coombs–Gell classification in four subgroups, called type I – IV reaction. Due to the classification that is most commonly used by radiologists [15], only two entities (written in grey letters) should exist.

**Table 1.** Four (I–IV) types of Coombs–Gell allergic reactions, their pathophysiology, and clinical manifestations.

| Type | Description               | Pathophysiology                                                                                     | Clinical manifestation                                                                                                                                      |
|------|---------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I    | Immediate type reaction   | IgE mediated                                                                                        | Immediate (acute) reactions that occur with urticaria, angioedema, asthma/shortness of breath, tachycardia, hypotension, loss of consciousness, anaphylaxis |
| II   | Cytotoxic reaction        | IgM/IgG binds to antigens on cells which are subsequently destroyed by complement factor activation | Delayed (non-immediate) reactions that manifest as intravascular immune hemolysis or thrombocytopenia                                                       |
| III  | Immune complex disease    | IgG plus antigen = immune complex that deposit within vessel walls                                  | Delayed (non-immediate) reactions that manifest as vasculitis                                                                                               |
| IV   | Delayed cellular reaction | APC activate Th cells that induce the inflammation                                                  | Delayed (non-immediate) reactions that manifest as maculopapular exanthema, fixed drug eruption, toxic epidermal necrolysis                                 |

The need of a predicting test procedure on one hand, and the low predictive value of negative test results on the other hand prompted some clinicians to challenge patients with CM [23,50,54]. Unfortunately, the CM-challenge test has several disadvantages: (a) the challenge bears high risks for both recall of an anaphylactic reaction, and induction of an acute kidney injury; (b) due to these risks the challenge test should be performed by special experienced centers only during a 1-day hospital stay [44,50]; (c) the CM provocation test is not standardized (i.e. different CM test-doses, and different protocols are used); and last, but not least (d) this diagnostic tool was not always able to predict tolerable CM [50]. Especially the latter point is of clinical importance, and needs some explanations. The reason why the use of low-dose CM is not always able to clearly predict a non-tolerated compound could be due to the fact that it can theoretically induce a sensitization, and/or a low CM test dose is not able to induce adverse reactions in most patients. Interestingly, the challenge with small CM doses as predictor test is not new. Approximately 50 years ago, a similar practice was done: the manufacturers provided to each CM-flask a so-called test-dose (i.e. a small amount of 1-mL CM in a separate pharmaceutical vial). Since the provocation with such small amounts did not reveal all patients with an hypersensitivity, this kind of pretesting was given up. Instead of a controlled *in vivo* challenge test, we prefer intradermal tests up to undiluted CM, and/or the use of an *in vitro* challenge test, namely the basophil activation test. Immediate CM-hypersensitivity reactions are characterized by release of histamine /other biogenic amines from basophilic granulocytes and by release of tryptase from mast cells. The basophil activation test is a complete safe alternative as compared to the high-risk *in vivo* challenge test. Currently, the basophil activation test can be used to both confirm culprit CM, and to find individual nonreactive alternate CM [57,58].

Formerly, after the application of hyperosmolar iodinated CM, a substantial complement activation could be detected in some patients with adverse reactions, while the effect of modern non-ionic low or iso-osmolar compounds is less prominent [59–61]. This could be another hint for the notation that ionic, and non-ionic iodinated CM might have different capacities in the elicitation of allergy reactions.

Delayed/non-immediate CM-hypersensitivity reactions are tested by delayed readings (24–96 h) of the intradermal test, and by patch tests with undiluted CM and test readings after 48 and 72 h [35,44]. Negative tested CM can be used as alternate compounds that should be tolerated by the patient [35].

*Nomen est omen* (the name is everything) – as aptly stated in Latin. To call all hypersensitivity reactions ‘allergy like’ without any diagnostic procedures clearly ignores the aforementioned findings, makes a formal allergy workup senseless, and inhibits further scientific research. Taken together, drug reactions in general, and CM reactions in particular may be either allergic or non-allergic. Since CM are among the drugs the most common elicitors of anaphylactic reactions, and exanthemas [44], an effective prophylactic management on the basis of a general accepted classification/nomenclature would be desirable. Therefore, the term ‘allergy like’ should be replaced by ‘hypersensitivity’ when the underlying reaction has not been tested [48]. Only a formal allergic workup can determine whether a reaction is either allergic or non-allergic.

### 3. Myth 2: an allergic reaction is not possible at initial CM exposure

One typical feature of allergic reactions is the fact that the initial exposure to an allergen induces sensitization and only subsequent contact elicits the clinical symptoms. Therefore, clinical symptoms usually do not occur at the initial exposure. Surprisingly, hypersensitivity reactions have been reported even at the initial administration of either iodinated CM or gadolinium-based contrast agents [19,41,51,53–55,62]. Although systemic analyses are currently missing, there are several papers that provide a positive skin test result in single cases or patient groups with CM-hypersensitivity at their first CM contact [19,41,51,53,54]. More than 30% of skin test-positive reactions can occur at the initial CM administration [51]. One clinical example is a patient in our department who for the first time in his life received a gadolinium-based contrast agent for magnetic resonance imaging (MRI). Shortly after starting the gadolinium-based contrast agent-injection, he recognized a feeling of warmth, itching, shortness of breathing, and finally he developed generalized urticaria. Intradermal testing with a  $10^{-2}$  gadolinium-based contrast agent dilution revealed a positive reaction against the culprit CM (Figure 2).

Both immediate [51,53–55,62], and non-immediate (delayed) adverse reactions can occur after the initial exposure to an agent [41,51], and reactions of all grades of severity, including anaphylaxis are possible [34,51,53,55].

CM allergies even at the initial exposure are discussed controversially. Some authors argue that this observation supports the non-allergic nature. But on the hand, it is tempting to speculate that a (silent) sensitization against an unknown cross-reacting molecule could contribute to the presence of a CM-allergy upon initial CM administration. Research on this topic is still ongoing and future results are greatly anticipated.

### 4. Myth 3: an iodine allergy is an important consideration prior to iodinated CM administration

Patients who are to undergo contrast-enhanced examination are commonly asked as to whether they have an ‘iodine



**Figure 2.** Results of an intradermal skin test following subcutaneous administration of a  $10^{-2}$  dilution of gadobutrol (white arrow) with wheal and skin redness (erythema) in a patient with no known previous exposures to GBCA. As mentioned in the text, these results contradict the myth that CM-induced allergies cannot occur following the initial exposure to CM.

allergy.' Although neither the ACR nor ESUR guidelines list an 'iodine allergy' as a risk for CM-reactions [4,5], such terminology still exists in routine practice. 'Iodine allergy' in the context with iodinated CM is the most prevalent radiological myth. As the term is prone to induce confusion, it is recommended to be avoided. During the past 10 years, it has been pointed out that the iodine content of iodinated CM is not responsible for observed adverse reactions [63,64]. Moreover, a true allergy to iodine has not yet been demonstrated; in other words, an 'iodine allergy' does not exist. One should realize that iodine is naturally taken up by the thyroid gland. Therefore, having an allergy to it would require patients to be constantly reacting to iodine. Last but not least, the misused term 'iodine allergy' comprises not only allergies against iodinated CM, but also against iodinated antiseptics such as polyvinylpyrrolidone-(PVP)-iodine, against the drug amiodarone, and very surprisingly even against fish and shellfish [65–69]. The reason for this terminology was the wrong assumption that 'iodine' would be the culprit agent. Therefore, it was once recommended either to avoid iodinated CM in patients with shellfish allergy or to prophylactically pretreat such individuals with antiallergy drugs. This recommendation is no longer valid, because it became evident that shellfish allergy is due to a reaction of the immune system against the muscle protein tropomyosin, while the reaction in patients with iodinated CM allergy is directed against the contrast molecule, but not against the iodine part [63,65,67,70]. Neither shellfish and iodinated CM, nor polyvinylpyrrolidone (PVP) iodine and iodinated CM have a common molecular architecture so that immunological cross-reactivity can be excluded. Due to these facts, many authors have recommended avoiding the term 'iodine allergy,' but seemingly without effect [63,65,67,70–73]. Like many myths, that of an 'iodine allergy' persists tenaciously in the minds of physicians.

What is the significance of an hypersensitivity reaction to amiodarone in a patient with a known iodinated CM hypersensitivity [74]? Does this support the concept of 'iodine allergy'? Not at all, because iodinated CM allergy or – hypersensitivity and amiodarone allergy are distinct clinical conditions and due to the fact that individual patients may suffer from multiple different allergies.

Moreover, clinical reliance on the concept of 'iodine allergy' for decision-making is not only formally incorrect, but can result in increased risks for adverse events under routine conditions as demonstrated by the following two cases.

A 68-year-old female diagnosed with a so-called 'iodine allergy,' and arranged for a CM-enhanced radiological exam acquired a local skin reaction after the use of PVP-iodine. Her 'iodine allergy' had been falsely interpreted as iodinated CM allergy. She was treated with PVP-iodine, and subsequently experienced a PVP-iodine hypersensitivity reaction. Luckily she only suffered from a cutaneous reaction considering that anaphylactic reactions against PVP-iodine have also been observed [75]. This case demonstrates that the term 'iodine allergy' is not a useful concept to prevent adverse events/hypersensitivity reactions.

The second case is a 39-year-old female patient with PVP-iodine (Betadine®) allergy. The diagnosis of iodine-containing antiseptic-allergy was stepwise modified from visit to visit to

'iodine-allergy.' Due to the 'iodine allergy,' the patient was premedicated prior to administration of iodinated CM. Ultimately the examination was canceled due to the 'iodine allergy.' This case is an example where the ambiguity of the term 'iodine allergy' led to inappropriate premedication of a patient with ultimate cancellation of a clinically appropriate radiological examination.

In addition to these anecdotal cases, a clinical study provided also evidence for the assumption that the term 'iodine allergy' is incomplete and potentially dangerous leading to uncertainty in clinical management and sometimes to ineffective prophylactic measures [76].

## 5. Myth 4: premedication is helpful in all circumstances

Patients with a history of a CM-hypersensitivity reaction are at increased risk to experience an adverse event following CM re-exposure. To prevent such reactions, patients with a previous history of a CM reaction often receive drug pretreatment. Although this kind of prophylaxis has been used for more than 40 years [77], currently there is no established gold standard for this procedure. Moreover, premedication does not guarantee complete suppression of all possible CM-related reactions. This means that pretreatment with corticosteroids, anti-H1 medications, and the use of non-ionic CM do not completely prevent anaphylaxis [4,5,25]. So-called breakthrough reactions of all severity grades have been observed in 1.2% up to 40% of pretreated patients [10,78–80]. These reactions can occur after non-ionic or ionic iodinated CM administrations as well as after the administration of gadolinium-based contrast agent.

Pretreatment drugs themselves can induce adverse drug reactions (ADRs). Independent of their efficacy to suppress CM adverse events, both glucocorticoids and antihistaminics are able to elicit adverse reactions including drug eruptions and anaphylactic reactions [81–85]. Due to the same immunological mechanism, the clinical features of the adverse events induced by the premedication are indistinguishable from symptoms caused by CM.

So have steroids been reported to cause facial flushing accompanied by feelings of warmth [52], to worsen asthma, and to induce allergies of immediate or non-immediate (delayed) onset, and mild-to-severe grades [86–89]. Besides, glucocorticosteroids should be used with caution in patients with diabetes mellitus, osteoporosis, and infections [90,91].

The sedative effects of the first-generation H1 antihistamines (e.g. hydroxyzine, diphenhydramine, clemastine) are well known. Less known are other adverse effects such as cardiotoxicity, severe arrhythmia, and induction of allergy including anaphylaxis that can be induced by H1 blockers [92–94]. H2-antihistamines (e.g. ranitidine) also have the potential for adverse events including anaphylaxis [95].

Last but not least in routine practice, patients with previous ADRs may refuse premedication [52]. In such cases non-contrast radiologic examinations are the best choice for evaluation. Another alternative is an individual management program based on a formal workup of the patient's allergies [24,52].

## 6. Myth 5: interleukin-2 (IL-2) therapy is a risk for iodinated CM adverse events

So-called biologics are modern treatment options. In addition to interleukins and interferons, tissue-specific monoclonal antibodies and other biologics (e.g. tumor necrosis factor  $\alpha$ ) are used to treat different forms of diseases including oncologic conditions. Every therapeutic option yields a theoretical risk for an adverse event/hypersensitivity reaction when combined with (iodinated) CM. In the 1990s, recombinant interleukin-2 (rIL-2) (Proleukin®)/Aldesleukin raised the suspicion for such a risk [96,97]. Six years after the clinical approval of Proleukin®, Zukiwski et al. reported an increased incidence (8/28 equates to 28%) of hypersensitivity to iodinated CM in IL-2-treated patients [97]. In the same year, Oldham et al. published a series of 22/200 patients (11%) on IL-2 therapy who demonstrated a so-called 'recall' reaction (an iodinated CM-induced adverse reaction that resembles adverse IL-2-related reactions) after iodinated CM injection [98]. Shortly afterward, another report on complications in IL-2-treated patients described completely different reactions to iodinated CM (e.g. nonspecific reactions such as cardiorespiratory arrest, thrombosis/embolism, bleeding/hematoma, and left gastric artery extravasation) [99]. Throughout the early 1990s, a few additional cases were published [100,101] (Figure 3). High- and medium-dose rIL-2 [97] and even local IL-2 treatment [101] with a low concentration of absorbed rIL-2 were identified as potential inducing factors. Finally, two clinical studies revealed IL-2 and iodinated CM-associated side effects in 20/170 (11.8%) and 8 of 74 iodinated CM administrations (11%) [102]. Subsequently, no case report nor clinical study regarding this phenomenon has been published (Figure 3). This is surprising, because both the number of IL-2-treated patients and of contrast-enhanced computed tomography (CT) examinations have continuously increased [3] since the inception of IL-2 therapy in 1984. This clear discrepancy prompted a literature search published in 2009 [96]. Moreover, our own review of patients treated with

IL-2 who underwent contrast-enhanced CT found no patients with an adverse event (unpublished data). The aforementioned reports with IL-2 are likely attributable to the so-called 'Weber effect.' In 1984, J.C.P. Weber published his observation that when a new drug is introduced to the market, associated adverse events are regularly overestimated [103].

Current review articles and ACR/ESUR guidelines on CM persist in listing IL-2 treatment as a risk factor for adverse reactions to iodinated CM [4,5,104–108]. While some papers/web resources point to an increased risk of delayed hypersensitivity reactions, others do not explain what kind of reaction pattern is expected [4,5,105–108].

'Adverse reactions' described in IL-2-treated patients consisted of a broad range of clinical features such as fever, chills, malaise, flu-like symptoms, dizziness, joint pain, headache, nausea/vomiting, skin rash, pruritus, hypotension, transient rises in serum creatinine levels, and oliguria [97,98,100,102]. Because these adverse events resembled side effects seen under IL-2 without any additional iodinated CM-injection, they were labeled as 'recall reaction' [98]. Since adverse reactions occurred 1 h or later after the iodinated CM-injection, they also were referred to as 'delayed reactions' [102]. Instead of a uniform term, the authors used different terms such as 'recall reaction,' 'hypersensitivity-reaction,' 'delayed reactions,' and finally simply 'adverse reactions' [97,98,102] complicating the situation.

Last but not least, it became evident that both non-IL-2- and IL-2-treated patients displayed the same reaction profile [102]. This fact in concert with the narrow time frame in which case reports and clinical studies have been published argues for the overestimation of IL-2 as a risk for iodinated CM adverse events.

Nevertheless, the association of IL-2 with an increased risk for adverse reactions after iodinated CM injections continues to pervade the medical community. This could lead to unnecessary prophylactic actions in patients on IL-2 therapy,

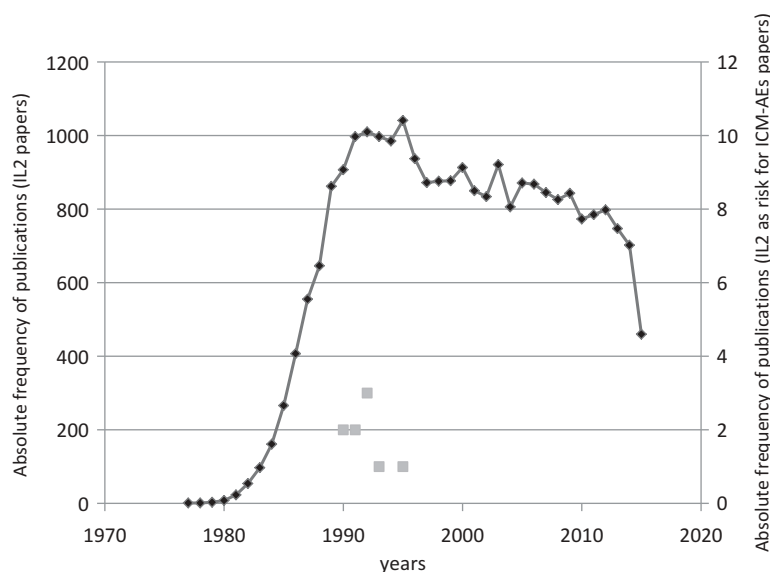


**Figure 3.** The diagram shows both the increasing publication of papers describing IL-2 treatment (black dots and left y-axis), and in parallel some papers dealing with IL-2 as risk for the acquisition of CM-AEs (light grey squares and right y-axis).

including premedication or avoidance of iodinated CM. In other words, the supposed increased frequency of iodinated CM adverse effects under IL-2 treatment seems to be attributable to the so-called Weber effect [103].

## 7. Conclusion

- CM can induce hypersensitivity reactions (also called type B reactions) that may be either true allergy or 'allergy-like' reactions. Such differentiation can be done on the basis of an allergy-work-out. Moreover, allergy testing provides a differentiation in culprit/positive, and alternate/negative tested compounds.
- Although unusual allergic CM reactions can arise at the initial CM exposure, it is also possible that an unknown cross-reacting agent is responsible for this phenomenon.
- The term 'iodine allergy' should be omitted, because such kind of allergy implies in its sense of word that it is an allergy against elemental iodine, which would be lethal. The iodine content of iodinated CM is not responsible for the elicitation of ICM allergy. Cross-reactions between completely different substances such as shellfish/fish and iodinated CM or PVP-iodine disinfectant and iodinated CM do not exist. Therefore, recommendations to withdraw iodinated CM in patients with either shellfish/fish or PVP-iodine allergy should no longer be propagated.
- Antiallergy premedication (i.e. H1 antihistaminics and corticosteroids) is able to suppress mild and possibly moderate type I reactions that manifest with urticaria, angioedema, tachycardia, and difficulties to breath. However, premedication will fail to completely suppress other reactions such as anaphylactic shock, maculopapular exanthema, and fixed drug eruption for example.
- Shortly after its introduction in the 1990s, interleukin-2 therapy has been suspected as risk/trigger for iodinated CM adverse events. Several decades afterwards, and on the basis of an intense use of interleukin-2 for cancer patients, it became evident that this causal connection is unlikely to exist.

## Funding

This article was not funded.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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