

Hypersensitivity reactions from antineoplastic agents

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Abstract

Antitumor drugs, like any other therapeutic agent, have the ability to incite hypersensitivity reactions. Certain of such drugs (e.g., L-asparaginase and taxol) cause reactions with great enough frequency to be a major impediment to repetitive use of the drug. Very few antitumor drugs have not had at least one reported instance of causing a hypersensitivity reaction. Most reactions are of the type I category in the Gell and Coombs classification, but there also are instances of types II, III, and IV reactions caused by many of the antineoplastic agents.

The mechanisms of such reactions have been poorly evaluated in many reports. In analyzing a hypersensitivity reaction in a patient being treated for cancer, one should document that the antitumor drug is indeed the offender, and not an ancillary drug or a formulation product that is being used. There are many tests that evaluate the source and mechanism of hypersensitivity reactions. This article reviews the current information on hypersensitivity reactions to antineoplastic drugs and provides a logical approach for their assessment.

Introduction

Cancer chemotherapeutic agents have the ability to interfere with some molecular processes vital to the life of the cell. Cells that are actively replicating can be sensitive to such lethal interference with their enzymatic reactions. Unfortunately, the unselective nature of most cancer chemotherapeutic agents causes them to seriously impede vital metabolic reactions in actively replicating normal tissues as well. Therefore, unpleasant and sometimes life-threatening side-effects occur. Side-effects common to most agents are alopecia, myelosuppression, and gastrointestinal disturbance.

Whenever one begins chemotherapy in a patient with cancer, one must provide a full recitation of possible side effects. In the early 1970s, when one of us (RBW) was beginning his career in medical

oncology, some patients would listen to this recount of possible side effects and then respond with the following question: 'I am allergic to _____ (e.g., penicillin); do you think I will be allergic to any of these cancer drugs?' The answer frequently given was that except for one rarely-used drug (L-asparaginase), allergic reactions to cancer chemotherapeutic agents were very rare, in fact almost unheard of, and were therefore unlikely to occur. This stock answer was changed in 1977 when a patient (treated by RBW) suddenly collapsed and had a cardiac arrest a few minutes after receiving an intravenous injection of melphalan. Fortunately, this patient was resuscitated, and he recovered from this anaphylactic reaction. This event incited an interest in allergic reactions induced by such cancer chemotherapy and culminated in the publication of several reviews on the subject [1, 2].

In the past decade oncologists have learned that most available chemotherapeutic agents can produce hypersensitivity reactions (HSR), and a substantial minority cause reactions in up to 5% of patients receiving the drug. There are now two agents (L-asparaginase and taxol) for which HSRs are frequent enough to be a major form of dose-limiting toxicity. The observation and reporting of HSRs from such drugs has spurred some research into the mechanism of the toxicity, and some attempts to ameliorate or prevent the problem. However, the mechanism of such reactions remains unknown for most chemotherapeutic agents, and it is rarely possible to prevent them.

This article will update clinical information about HSRs from cancer chemotherapeutic agents and expand the list of drugs known to cause such toxicity at least sporadically. We will focus on what is known about the mechanism of these reactions and suggest leads for research activity. The definitions of hypersensitivity reactions, the classification terminology, and the various clinical manifestations have all been previously addressed [1, 2].

Reports of HSRs from anticancer agents are usually prepared by oncologists, not allergists. Although many investigators use the Gell and Coombs classification [2], they frequently misuse the terms anaphylaxis and anaphylactoid reactions. Anaphylaxis is an immediate (Type I) hypersensitivity reaction characterized by vasodilatation at the level of the capillary or post-capillary venule, and smooth muscle vasodilation. Widespread vascular dilatation leads to decreases in systolic blood pressure that can reach shock levels. The main mediator for such anaphylactic reactions is IgE, but antigen-antibody reactions involving IgG or IgM are sometimes responsible.

Anaphylactoid reactions have identical clinical manifestations to Type I reactions, but they are differentiated because they do *not* involve IgE in the release of mediators. The inciting drug may cause the release of vasoactive substances from basophils and mast cells through a direct effect on the cell surface, or via activation of the alternative complement pathway with resultant production of anaphylatoxins. The term anaphylactoid reaction has no relation to the degree of symptoms, but

instead indicates the mechanism involved in producing the reaction. Some authors referenced in this paper have used this term incorrectly.

L-asparaginase

L-asparaginase remains the antitumor drug that is most likely to cause HSRs. This drug is only used to treat some uncommon cancers, such as acute lymphocytic leukemia and its clinical variants. HSRs are a major dose-limiting side-effect, occurring in a consistent 12%–20% of patients receiving the drug as part of combination therapeutic regimens [3–5]. This high rate of HSRs is undoubtedly related to the fact that L-asparaginase is a polypeptide of bacterial origin.

The manifestations of L-asparaginase hypersensitivity are usually those of Type I reactions. Pruritus, abdominal cramps, dyspnea, and agitation are the usual symptoms. Urticaria, angioedema, rash, laryngospasm, bronchospasm, and hypotension are the signs of such toxicity. These symptoms and signs can progress to full anaphylaxis, with shock and loss of consciousness and, occasionally, death. Evans *et al.* [3] studied 36 patients with L-asparaginase reactions. Sixteen (44%) patients had severe reactions that included the presence of respiratory distress and/or hypotension with >20 mm Hg decrease in systolic blood pressure (i.e., anaphylaxis). The other patients also had Type I reactions, but without hypotension [3]. A number of factors enhance the risk of L-asparaginase induced HSRs [2]. L-asparaginase is now rarely used as a single agent; it is most often administered concomitantly with or sequentially to vincristine-prednisone and perhaps other agents. Some evidence [1, 2] suggests that vincristine and prednisone reduce the frequency of reactions. Intramuscular administration also appears to reduce the frequency of anaphylaxis [2, 6]. However, milder degrees of Type I reactions can still occur. The postulated explanation for a reduced incidence of severe reactions using the intramuscular route of administration is that peak blood levels of drug are lower [2], but the use of a drug dose as high as 25,000 IU/m² may produce peak blood levels high

enough to counteract the advantage of intramuscular injection. Despite the use of intramuscular injection and concomitant vincristine-prednisone and other agents, severe reactions can still occur with appreciable frequency, as seen in the study by Clavell *et al.* [4], in which 19% of patients showed allergy to L-asparaginase. This high rate may be explained by the use of a L-asparaginase dose of 25,000 IU/m².

Another factor that increases the risk of reactions is previous exposure to L-asparaginase [2]. A study by Albo and colleagues [7] emphasizes this point and shows that immunogenicity with this drug is long-lasting. Albo *et al.* [7] treated 92 patients with intramuscular L-asparaginase as consolidation therapy beginning 3 yr after the last L-asparaginase dose. None of these patients had sustained a previous HSR to L-asparaginase. Despite concomitant treatment with vincristine-prednisone, 35% of these patients developed Type I HSRs, a third of them from the first drug dose.

The mechanism of L-asparaginase-induced HSRs is not well understood. Khan and Hill [8] provided good evidence that IgE mediates the reaction in at least some cases. In five patients who experienced a HSR, the reactivity was mediated by a skin sensitizing IgE, as demonstrated by skin testing and Prausnitz-Kustner reaction studies [8]. More recently, Fabry and colleagues [9] showed that patients sustaining HSRs had evidence of complement activation with elevated levels of the C3 split product, C3d. These investigators suggested that IgG or IgM immune complexes initiate the complement activation process and thus mediate the reactivity.

Despite various attempts to detect reactivity before a dose of L-asparaginase is administered, there is no reliable way to predetermine which patients will sustain a HSR. Intradermal skin testing can give both false negative and false positive results [1]. Test doses of small amounts of drug also are valueless. In one study [3] an intravenous test dose rarely produced a reaction and was falsely negative in most patients who developed a HSR. Unfortunately, one must approach each dose to be administered as the one that could incite a serious HSR, and be prepared to quickly reverse any reac-

tion with appropriate medication. This means that anti-anaphylaxis medication should be close at hand, and that the patient should be observed for reactions during the hour after each dose injection. Intramuscular drug administration is preferable in order to minimize the risk of anaphylaxis. However, individual drug doses over 20,000 IU can cause much patient discomfort at the injection site and intravenous administration may be necessary.

When a HSR to the *E. coli* derivative occurs, the *Erwinia* derivative can be used as a substitute. *E. coli* type L-asparaginase has been marketed for some eight years, but the *Erwinia* derivative is still available only from the National Cancer Institute (NCI) under the Group C category of investigational drugs. The NCI has attempted to interest a pharmaceutical firm in seeking Food and Drug Administration approval for marketing this derivative under the auspices of the Orphan Drug Act, but this has not been accomplished to date. For the present, the NCI will continue the task of supplying this analogue for individual patient use.

Until the past few years, cross-reactivity between these two agents was reported to be rare. A patient who was reactive to one derivative was unlikely to react to the other derivative. However, Evans *et al.* [3] recently observed that 26% of patients sustaining HSRs to the *E. coli* derivative also had reactions to the *Erwinia* derivative. Two of these patients reacted to the first dose of the *Erwinia* derivative. Similarly, Clavell *et al.* [4] reported that 9 (16%) of 54 patients reacting to the *E. coli* derivative also reacted to the *Erwinia* type. These findings indicate that HSRs are still possible in a large minority of patients changing from one L-asparaginase form to the other. Precautions for HSRs must be taken when administering the substitute derivative, because not only is there the possibility that cross-reactivity will produce another HSR with the first dose, but also that new antibodies to the substitute can develop just as readily as they did to the original form of L-asparaginase.

Taxol

Taxol is an investigational antitumor agent undergoing Phase II trials. Phase I trials were recently completed. It is derived from the bark of an evergreen shrub called the Western Yew (*Taxus brevifolia*). HSRs were a major toxicity in the initial Phase I clinical trials, and they have proved to be one obstacle to the speedy accomplishment of phase II trials.

Kris and co-workers [10] observed HSRs in three of five patients receiving 190 mg/m² or higher doses administered over 3 hr. These reactions were characterized by skin erythema, dyspnea, and abdominal pain. One patient had anaphylaxis, shock, and a cardiorespiratory arrest from which he died. These investigators [10] considered HSRs to be the dose-limiting toxicity and a deterrent to the use of a dosing schedule of every 3 wk.

Other investigators reporting phase I trials noted HSRs at lower doses of taxol [11, 12]. By early 1985 12 (11.7%) of 102 patients treated with taxol had sustained HSRs [13]. These reactions consisted of dyspnea, hypotension, and skin erythema, and all occurred within a few minutes of starting the drug infusion. Six of these 12 reactions occurred during the first exposure to the drug [13].

The cause of these reactions could be either the taxol, the drug vehicle (Cremophor EL), or a combination of both compounds, but the mechanism has not yet been elucidated.

In order to reduce the frequency of these HSRs, investigators using this agent have been advised to give a small test dose infusion for 30 min and to prolong the total infusion duration to 4 or 5 hr. In addition, patients are premedicated with prednisone and antihistamines. This premedication markedly reduced the incidence of such reactions in one study [14].

It is not known whether taxol will ever have a role as an effective antitumor agent. Until the HSR problem is better controlled, widespread study of this agent will not be possible. A 10% incidence of life-threatening HSRs, with an occasional death, is too high for the safe use of taxol, especially when about one-half of the episodes occur from the first drug dose.

Elliptinium

Elliptinium is a compound that is classified as investigational in the United States, but is marketed in some European countries for the treatment of breast cancer. It represents a new class of synthetic compounds whose parent structure was derived from a plant called ochrosia. HSRs in the form of type II reactions have been a major toxicity problem.

Criel *et al.* [15] first observed intravascular hemolysis induced by this drug. In one patient [15] this reaction caused renal failure, requiring temporary dialysis. Subsequent studies indicated that hemolytic anemia could occur in up to 7% of patients treated with elliptinium [16]. The manifestations of these HSRs have been hypotension, flank pain, dyspnea, restlessness, rigors, decrease in serum hemoglobin, and hemoglobinuria (black urine). Other laboratory abnormalities such as decrease in serum haptoglobin, rise in serum bilirubin, and free hemoglobin in plasma have been observed [15].

Type II HSRs can result in hemolysis through the development of antidrug antibodies that react with antigen fixed to red cell surfaces. This binding initiates the sequence of complement activation, resulting finally in red cell lysis. Type II reactions induced by antitumor drugs are a rare event [17], and elliptinium is the only drug that causes this problem with any frequency. Criel and co-workers [15] showed that an IgM antibody mediated the reaction. This antibody agglutinated normal red cells only in the presence of elliptinium. Further studies of the antibody demonstrated that it appeared in 20%–40% of patients receiving weekly drug administration, and that as many as two-thirds of patients with such antibody developed hemolysis [17]. None of the patients without antibody developed clinical evidence of hemolysis. Since weekly drug administration appeared to induce antibody formation and cause the high rate of hemolytic episodes, a different dosing schedule of daily drug for three days every three weeks was tested by Mondesir and colleagues [18]. They also prospectively tested for the presence of antibody. Hemolysis did not occur, and antibodies did not

develop [18]. Therefore, it is recommended that patients being treated with elliptinium have serial determinations of antibody titers. If the titer reaches 1 : 32, the drug should be discontinued. The titers will decline in a few weeks [18], and no hemolysis should occur.

In addition to causing the more common Type II reactions, elliptinium also appears to cause Type I reactions. Dyspnea, hypotension, tachycardia, and chest pain have occasionally occurred in the absence of intravascular hemolysis [19]. These problems quickly subsided when the drug infusion was stopped. Prolonging drug infusion to 3 or more hr seemed to reduce the severity of these abnormalities. However, two deaths that occurred during drug infusion have been reported [20, 21]. It is uncertain whether these deaths originated from cardiac toxicity or were initiated through some form of Type I HSR; the latter is a good possibility. One patient [20] had received 9 previous drug doses; the other patient [21] had received 12. IgE antibody could have been stimulated by the previous elliptinium doses, and an anaphylactic reaction could have been precipitated. If Type I reactions can occur, it is puzzling as to why prolonging the infusion time reduces their incidence.

Alberici and co-workers [22] have attempted to identify the immunogenic determinant of elliptinium. They demonstrated that the quaternary ammonium-containing ring in the elliptinium structure plays a major role in antigenicity, but the haptogenic mechanism is still not known.

Epipodophyllotoxins (teniposide and etoposide)

In the previous reviews of HSRs from antitumor drugs [1, 2], teniposide was clearly implicated in the reactions of up to 11% of patients treated. Its congener etoposide, on the other hand, rarely seemed to cause such reactions [1]. Recent investigations have clarified this situation.

O'Dwyer *et al.* [23] surveyed both the literature and investigators using teniposide to obtain a firm estimate of the incidence of HSRs. They found that the overall incidence was 3.6% to 6.5%. They further found that 82% of the patients sustaining a

HSR had a brain tumor or neuroblastoma, whereas only 25% of all patients treated with teniposide had either of these diagnoses. These data are further corroborated by a study by Hayes *et al.* [24] (cases included in review by O'Dwyer *et al.*) comparing the incidence of HSRs in patients with neuroblastoma versus patients with leukemia or lymphoma. The incidence in the neuroblastoma group was 13%, whereas it was less than 2% in the other group [24]. Why patients with craniospinal tumors or neuroblastoma are more likely to have HSRs from teniposide is unknown. As O'Dwyer *et al.* [23] point out, it is not a drug-dose relationship, because higher doses are used for treatment of lymphoid malignancies. Neuroblastomas produce excess catecholamines, and these vasoactive substances may provide a milieu in which HSRs from teniposide are more likely.

Etoposide has also been clearly demonstrated to cause HSRs [25, 26]. The incidence of this toxicity is difficult to determine because of the anecdotal nature of these reports. Only poorly described, sporadic cases [27–29] are reported in series of patients treated with this drug. This fact may be due either to under-reporting or to less frequent reactions than with teniposide. Although under-reporting could account for part of the lower number of cases, HSRs do not occur at an incidence of up to 13%, as in some series of patients treated with teniposide [24]. A reasonable estimate of the incidence with etoposide is 1%–3%. Interestingly, not only does etoposide induce fewer HSRs, but there also seems to be a lack of cross-reactivity between the two agents. Hayes *et al.* [24] noted that five patients reacting to teniposide did not react when etoposide was administered as a substitute.

The symptoms and signs of HSRs from either drug are generally those of Type I reactions. Dyspnea, wheezing, urticaria, pruritus, hypotension, tachycardia, and diaphoresis have all been observed [23–29]. Many of these episodes have occurred from the first drug dose. These abnormalities usually begin soon after initiating the drug infusion and can be controlled by stopping the infusion and medicating with steroids and antihistamines. Some patients [23–25] can be retreated with the drug successfully if they are premedicated

with steroids and antihistamines, or in some cases if the infusion time is prolonged [23, 30]. There have been no reported deaths.

In one case, a rare Type II hemolytic reaction was reported secondary to teniposide [31]. A drug-dependent IgG was found to mediate the reaction. Despite an incidence of up to 13% for Type I HSRs due to teniposide, only this single case of Type II reaction has been published.

The mechanism of HSRs from these drugs is unknown, but it is unlikely to be an IgE-mediated phenomenon because of the frequency of reactions during first drug exposure. Equally unknown is the reason for the lower rate of reactions from etoposide. The minor variance in chemical structure of the two agents suggests that such differences are not the explanation. A possible reason is the difference in drug formulation: teniposide is formulated with Cremophor; etoposide is formulated with Tween 80. (This aspect will be discussed in a subsequent section.) Another possibility is that teniposide produces a reactive metabolite in higher concentration than etoposide.

Cisplatin and its analogues

Platinum salts were first observed to produce bronchial asthma among platinum refinery workers in 1945 [32]. Subsequent reports confirmed that platinum-containing compounds could produce Type I HSRs [33]. Thus, one would expect that when used clinically, cisplatin and all its analogues would have the ability to cause HSRs. In several series, cisplatin reactions have been reported in 1% and up to 25% of cases [1, 2]. A reliable overall incidence has never been determined, but 5% or slightly less is probably reasonable.

Intravenous cisplatin can cause HSRs, and so can drug instilled intravesically for bladder cancer. In fact, the incidence of such reactions appears to be higher than with intravenous administration. In a study of intravesical use by Blumenreich and co-workers [34], 5 of 24 patients had drug related rashes and another patient had a severe anaphylactic reaction, for an overall incidence of HSRs reaching 25%. Denis [35] reported that 7 (10.4%)

of 67 patients sustained anaphylactic reactions from intravesical cisplatin. The minimum number of repetitive drug installations before a reaction occurred was eight, given over 4 months. There was an incidence of 14% among patients who received a minimum of 4 months of treatment. From these data one could conclude that cisplatin administered intravesically (presumably involving systemic drug absorption) is more allergenic than when given intravenously. However, there is no logical explanation for such a difference. It is of interest that studies of cisplatin administered intrapleurally or intraperitoneally have not shown a correspondingly high incidence of HSRs [36]. It is puzzling that cisplatin administered in the bladder is systemically allergenic, whereas drug administered in body cavities (presumably with no less total drug absorption) is not.

The manifestations of the Type I HSRs to cisplatin, whatever the route of administration, are anxiety, pruritus, cough, dyspnea, diaphoresis, angioedema, vomiting, bronchospasm, rashes and urticaria, and hypotension. In contrast to HSRs related to L-asparaginase and taxol, there have been no reported deaths from cisplatin-induced HSRs. Prompt administration of glucocorticoids and antihistamines effectively aborts a reaction.

The mechanism of cisplatin-related Type I reactions has been investigated in only a few patients [37, 38]. Khan *et al.* [37] demonstrated that at least one case of cisplatin-induced reaction was mediated by IgE. In contrast, Wiesenfeld and colleagues [38] studied a patient who sustained a reaction for evidence of IgE-mediated reactivity, and found none. Others [39] have tested patients after reactions to cisplatin and have reported skin test reactivity to the drug.

When analyzing a patient who sustains a HSR, apparently from an antitumor agent, one must always consider the possibility that the drug formulation product or other drugs administered concomitantly are the allergens, and not the antitumor agent. (This issue will be discussed later in a section devoted to drug formulations.) In the case of cisplatin, other agents, such as antiemetics and diuretics, are frequently administered with it. Mannitol has apparently caused HSRs in rare instances

[40]; one patient [41] clearly had a HSR to mannitol (given to promote osmotic diuresis) administered just before cisplatin was to be given. It is possible that a few of the reported HSRs ascribed to cisplatin have been due to mannitol administered as an osmotic diuretic with the cisplatin.

Type II reactions with hemolytic anemia have been reported in several patients treated with cisplatin [2]. Anemia is a common toxicity from cisplatin and transfusions may be required [42]. However, the anemia is only rarely due to hemolysis. The most common form of anemia related to cisplatin is a slowly progressive, chronic process. A sudden decrease in hematocrit should raise a suspicion of a Type II HSR.

Analogues of cisplatin with nearly equivalent antitumor efficacy and lower rates of nephrotoxicity have been under clinical test recently. One of these analogues, carboplatin (CBDCA), is now marketed in some countries. Carboplatin and two other analogues, DACCP and iproplatin (CHIP), have produced HSRs with approximately the same frequency as cisplatin (i.e., 2.5%–10%). Bacha *et al.* [43] reported that one patient who had previously had a Type I HSR to cisplatin developed a similar reaction to carboplatin. Calvert and co-workers [44] reported that a patient had reactions from repetitive doses of carboplatin. Iproplatin caused similar Type I reactions in two series [45, 46]. A third analogue, DACCP, appears to be more allergenic than the other two. It has caused Type I reactions in 6.6% and 15% of patients, respectively, in two series [47, 48]. No Type II reactions have been observed from any of these analogues, but none has been as widely used as cisplatin. The mechanism of reactions from these analogues has not been studied in depth in any patient. DACCP will probably not be clinically tested further, and thus the puzzle regarding its apparent greater allergenicity will not be solved.

There is some lack of cross-reactivity between the two types of L-asparaginase, and the same appears true of these analogues. One patient known to be reactive to cisplatin was treated with iproplatin without further reactions [46]. However, the number of patients with known reactivity to cisplatin who are subsequently treated with an

analogue is too small to be certain of low or absent cross-reactivity. Since the platinum atom is presumably the antigen, cross-reactivity between these analogues is likely.

Procarbazine

Procarbazine has been known to produce HSRs since its initial clinical use two decades ago [49]. The most common manifestation of reaction is an erythematous maculopapular rash, but urticaria and angioedema have also been seen [50].

The incidence of such Type I reactions has never been well documented. The anecdotal nature of previous reports suggests that they are uncommon [1]. However, a recent trial indicates that reactions may be under-reported. Eyre *et al.* [51] noted that 11 (15.7%) of 70 patients treated with procarbazine had 'intense drug rashes' requiring the drug to be discontinued. This initial report was in abstract form; when this same study was published in a full article [52] there was no mention of these HSRs. In another study [53] by the same cooperative group, 3 (6.4%) of 47 patients treated with at least two courses of procarbazine had 'near fatal toxic epidermal necrolysis' that appeared to be due to procarbazine. No other data were provided regarding these apparent HSRs. Among 94 evaluable patients receiving procarbazine as part of the MOPP regimen for Hodgkin's disease in a Cancer and Leukemia Group B trial, 4 (4%) have had severe skin reactions requiring discontinuation of the procarbazine therapy (GP Canellos, personal communication). In the absence of more data from any of these trials, it is not possible to fully implicate procarbazine as the cause of the skin eruptions. Also, it has not been determined whether procarbazine can be readministered safely with concomitant steroids and antihistamines or in reduced doses.

Procarbazine can also produce rare instances of pulmonary toxicity with features of Type III reactions [54–57]. These patients have interstitial pneumonitis and eosinophilia in the peripheral blood and/or lung biopsy, and they improve with procarbazine withdrawal and corticosteroid therapy.

High fever and arthralgias can also occur [54,57]. In one case [56], two re-challenges with procarbazine promptly caused the same symptoms.

Although the incidence of procarbazine Type I reactions appears fairly high, no investigations into the mechanism of these reactions have been reported.

Cytarabine (cytosine arabinoside)

Cytarabine is a drug effective primarily in acute myelogenous leukemia. Although it has been in clinical use for over two decades, HSRs have only recently been observed with more than anecdotal frequency. This change may be due to the fact that the cytarabine doses now being widely used are 10–15 times greater than those used prior to the 1980s. Three distinct forms of HSRs to this drug have now been recorded.

The first form of HSRs is Type I, with dyspnea, chest pain, fever, maculopapular rash, urticaria, and hypotension [58–62]. The most common manifestation of reaction has been rash, but anaphylaxis has occurred in a few patients [58]. Although some authors have included conjunctivitis as a symptom of HSR to cytarabine [59–62], eye symptoms are not part of cytarabine-induced HSRs; they are caused by a keratitis induced directly by cytarabine [63].

Two groups of investigators have studied the mechanism of Type I reactions in two patients [58, 61]. In both cases, evidence was presented that implied the reactions were mediated by IgE. However, not all cases involve IgE, because at least one case [62] of drug-induced fever and rash occurred soon after beginning the first dose of cytarabine.

The Type I reactions described above can be initiated by moderate or high doses of drug. However, a second type of reaction induced by cytarabine seems to be generally dose related. First reported by Burgdorf *et al.* [64], this reaction is characterized by intense erythema of the palms and soles, with later development of bullae and desquamation [65–68]. Some patients also had fever, facial edema and erythema, and/or erythematous maculopapular rashes typical of a Type I reaction [65, 68, 69].

The incidence of this reaction has varied from 14% to 33% of patients treated with 1 gm/m² cytarabine doses or higher [65, 67], especially if eight or more doses at this level are administered. Some patients treated with conventional cytarabine doses of 100 mg/m² have also developed this acral erythema [68, 69]. The incidence at this lower drug dose level is not defined, but it is much lower than at high doses.

Skin biopsies have been obtained from some patients at the site of the reaction [65, 68]. The histologic abnormalities are nonspecific and are typical of drug-induced skin eruptions. The mechanism of these skin reactions involving primarily the palms and soles is not known. It may be a vasculitis that peculiarly involves certain small peripheral blood vessels. Although a Type III reaction is possible, this problem does not seem to be a HSR that fits neatly into any of the four major types. In fact, the relationship to drug dose suggests that these reactions are a result of direct epidermal toxicity.

The third type of cytarabine-induced reaction is a dermatosis, in which histologically there is a marked neutrophilic accumulation around the dermal sweat glands. First reported by Harriat and colleagues [70], this entity of neutrophilic eccrine hidradenitis has been observed by others [71], and appears to be induced by cytarabine. The skin lesions are erythematous plaques or nodules that may be tender and are not pruritic.

The mechanism of this apparent drug-induced problem is not known. Although the first three reported cases [70, 71] were patients being treated with cytarabine, a reported case related to other antitumor agents [72] suggests that its genesis is not limited to cytarabine.

Anthracycline antibiotics

It is well known that daunorubicin and doxorubicin produce both Type I HSRs and a localized 'flare phenomenon' [1, 2]. Other analogues in this class, such as zorubicin (rubidazone) and aclarubicin (aclacinomycin), also produce these reactions [2]. As new anthracyclines are tested clinically, more

will be observed to produce such reactions. Edo-rubicin is the latest one to be added to this list [73]. The mechanism of these reactions to anthracyclines has not been investigated.

Although the cytotoxic antibiotic is undoubtedly the initiator of these HSRs, the manufacturer of doxorubicin believes that reconstitution of the drug with distilled water contributes to the frequency of the 'flare reactions'. Therefore, reconstitution of the desiccated drug in saline is recommended in preparation for administration. Solimando and Wilson [74] demonstrated that systemic Type I HSRs are not inhibited by use of saline reconstitution.

Cyclophosphamide and ifosfamide

Cyclophosphamide can rarely incite Type I reactions [1, 2]; when this has occurred, some of the cases have been severe, involving anaphylaxis and shock [75, 76]. The mechanism of these reactions has been studied, and it appears to be IgE-mediated. Some investigators have demonstrated skin reactivity using cyclophosphamide [77], but others [76] have found that in some cases the metabolite phosphoramide mustard could be the antigenic determinant, rather than the parent compound.

Ifosfamide is a cyclophosphamide analogue that has a similar spectrum of antitumor activity. It causes more chemical cystitis than cyclophosphamide, and it can only be used in conjunction with mercaptoethane sulphonate (mesna), which reduces the incidence of cystitis. Type I reactions have been reported [78, 79] when ifosfamide and mesna have been used together. The cases reported are few in number and poorly documented, so it is not possible to know which agent caused the reaction. Since mesna, by itself, has also been known [80] to cause HSRs, either ifosfamide or mesna could be the allergen.

Other alkylating agents

All the alkylating agents in clinical use have produced occasional instances of HSRs [1, 2]. Melpha-

lan given intravenously produces a relatively high rate of Type I reactions in comparison to the other such agents. In two large series of patients treated with intravenous melphalan, Type I reactions occurred in 2.4% and 4.8% respectively [81, 82]. In one of these studies [82], different groups of patients were also treated with intravenous melphalan plus other cytotoxic agents. It is surprising that none of these other patients sustained HSRs.

HSRs from oral melphalan have been reported only rarely [2]; it is unclear why the intravenous drug is so much more allergenic. Two cases have even been reported [81, 83] in which the patient was reactive to intravenous drug, but not to the oral form. Melphalan has variable absorption orally, but lower drug absorption cannot be the whole explanation. No work has been done to determine the mechanism of melphalan hypersensitivity.

Methotrexate

Methotrexate can produce occasional instances of Type I HSRs and interstitial pneumonitis with features of a Type III reaction [1, 2]. In addition, a case of hemolysis from a Type II reaction has been reported [84]. The Type I reactions are usually severe only when high dose methotrexate (plus citrovorum factor rescue) is used [1, 2]. The Type III reactions can occur with any degree of severity and do not have a relationship to drug dose. Although interstitial pneumonitis occurring with acute onset is the usual manifestation of the putative Type III HSRs, a vasculitis with skin lesions has been observed [85], and may also be a manifestation of a Type III reaction.

The mechanisms of the Types I and III reactions are unknown, but da Costa *et al.* [86] have demonstrated the presence of drug-protein-IgG complexes in three patients with Type I reactions. These complexes may have been involved in the HSRs. In the one patient [84] with hemolysis an IgG-3 antibody was demonstrated as the mediator of the reaction.

A toxic epidermal necrolysis can occasionally be induced by high dose methotrexate [87] and other

antifolates [88]. The mechanism of such severe skin reactions is not known, but they are probably not antibody mediated.

Bleomycin

Occasional severe hyperpyrexia (fevers $\geq 40^{\circ}\text{C}$) episodes occur from bleomycin, caused by the release of endogenous pyrogens [1, 2]. Some of these reactions cause hypotension and initiate disseminated intravascular coagulation with a fatal outcome [2, 89]. They occur most often in patients with lymphoma and are not dose related, as they have occurred from as little as 1 unit of drug or after as much as 60 units cumulative dose [1, 89]. These reactions would not be classified as HSRs. A few rare instances of reactions more suggestive of Type I HSRs have also been reported [90, 91]; one patient developed marked angioedema, and two had urticaria. The mechanism of these reactions is unknown.

Amsacrine

HSRs to amsacrine occur in less than 1% of patients treated [2, 92]. These reactions are manifested by rash, pruritus, urticaria, and angioedema. The mechanism has not been investigated.

Vinca alkaloids

HSRs to vinblastine, vincristine, or vindesine are very rare and are poorly documented. One case [93] in which a Type I reaction was ascribed to vincristine was confounded by the fact the patient was also receiving cyclophosphamide when the reaction occurred. Vindesine was substituted for vincristine and administered with cyclophosphamide; no further reactions occurred. No investigations were done to determine the mechanism of the reaction or to prove that vincristine was the cause. Vindesine was reported to cause a desquamating dermatitis in one patient, but further details were not provided [94]. One patient developed 'an al-

lergic reaction' to vinblastine, manifested by a maculopapular rash and dyspnea that recurred with rechallenge to the drug [95].

5-Fluorouracil (5-FU)

Only three cases of Type I HSRs have been reported secondary to 5-FU [96–98]: two patients had a severe hypotensive episode and the other had angioedema. Rechallenge with 5-FU in the latter patient caused a repetition of the reaction. None of these patients had any studies performed to determine the mechanism of reaction, although one patient [98] had skin testing with 5-FU and was reactive. 5-FU also causes a palmar-plantar dermatitis similar to cytarabine [99–101]. This condition begins with hand-foot paresthesias and progresses to erythema, swelling, and desquamation. The reaction was initially observed with high frequency in patients receiving continuous infusion 5-FU [99], but it has also been seen in at least one patient [101] receiving intermittent bolus therapy. The mechanism of this reaction is unknown.

Mitoxantrone

This agent has recently been added to the list of chemotherapeutic agents causing HSRs. Taylor *et al.* [102] reported three cases of HSRs, including one patient who developed shock. One patient was rechallenged with the drug and had a similar reaction. Another patient [103] has been reported to have an erythematous maculopapular rash secondary to mitoxantrone. No studies were done on these patients to determine the mechanism.

Dacarbazine

A single case of reaction to dacarbazine has been published [104]. The reaction was reproduced with drug rechallenge. The classification of this reaction would probably be an erythema multiforme, and thus a Type III. No studies were done to define the mechanism.

Mitomycin

Mitomycin is administered primarily intravenously, but is also instilled intravesically as a treatment for bladder cancer. Rare instances of reactions from both routes of administration have been reported.

Although the intravenous route is used more often than the intravesical one, the latter seems to result in more HSRs. Even more surprising is the site of such reactions related to intravesical instillation. Several groups [105–106] have observed palmar erythema and desquamation after intravesical mitomycin. Nissenkorn and colleagues [105] asked the reacting patients to wash their hands carefully after voiding post drug-instillation, thinking the reaction might be a topical drug effect. Hand washing seemed to prevent recurrence of the palmar reactions in two patients, but one patient had repeated generalized rashes with each drug instillation. Intradermal skin testing in five patients with such reactions [105, 106] was positive.

Diaziquone

Posada and colleagues [108] collected six cases of HSRs to this investigational agent. The manifestations were those of a type I reaction. Three patients were rechallenged with diaziquone and reacted again. Although no studies were done to define the mechanism of the reaction, the fact that all six patients had received at least three doses of drug suggests that an immunologic mechanism (perhaps IgE) was involved. The diaziquone solvent (dimethyl acetamide) was also thought to be a possible allergen [108], but this consideration was not evaluated.

Formulation compounds and excipients

We have focused so far on individual drugs, examining the frequency and kind of reactions and the mechanism of the reaction, if studied. Most of these reactions are clearly related to a chemotherapeutic drug. However, the diluent or excipient is

sometimes the cause, and the antitumor agent is falsely implicated. Thus, whenever evaluating the cause of a suspected drug reaction any diluents or excipients involved should be ruled out as the initiator of the reaction. A good example of the results of such efforts is provided by Wilson and colleagues [109]. Cytarabine preserved with benzyl alcohol caused a HSR that was later proven to be due to the benzyl alcohol and not the antitumor agent. Moreover, later treatment with vincristine and heparin, both preserved with benzyl alcohol, also caused HSRs. Since most reports of HSRs to cancer chemotherapeutic agents have not even attempted to rule out the diluent as the cause of the reaction, it is unknown how many reported reactions have falsely implicated the antitumor drug.

Occult reactions to diluents such as benzyl alcohol or mannitol (also used as an adjuvant diuretic [40, 41]) are probably uncommon, but this may not be true of two excipients. Cremophor EL and dimethyl acetamide (DMA). Cremophor, a solubilizer and emulsifier derived from castor oil that is a safe and effective stabilizer for many compounds, has been implicated as the initiator of HSRs to several drugs [110, 111]. Cremophor also may be the cause of HSRs to teniposide [23, 25] and taxol, and efforts are underway to replace Cremophor with a less allergenic compound. DMA, a solvent used in some antitumor agents, may be the cause of some HSRs to amsacrine and diaziquone. It could also contribute to teniposide reactions,

Table 1. Some examples of possible allergens in formulations of antitumor agents.

Chemotherapeutic agent	Diluent or formulation
Amsacrine	Dimethyl acetamide
Diaziquone	Dimethyl acetamide
Etoposide	Polysorbate (Tween 80)
	Benzyl alcohol
Procarbazine	Tartrazine dye
	Parabens
Methotrexate	Benzyl alcohol
Cytarabine	Benzyl alcohol
Mitomycin	Mannitol
Taxol	Cremophor EL
Teniposide	Cremophor EL

since it is also part of that drug's formulation. Table 1 lists selected antitumor agents and the various substances with which they are formulated. It is important to determine if the diluent or excipient is the cause of any HSR, because it is possible that a different formulation of the antitumor agent can be administered as a substitute, thus circumventing reactivity.

Evaluation of hypersensitivity reactions

From the previous discussion it is apparent that HSRs to antitumor agents are an important clinical problem. Almost all cancer chemotherapeutic agents have the ability to initiate HSRs at least in rare instances, and some cause reactions in a significant fraction of patients. Two of these agents have HSRs as one of their major dose-limiting toxicities. It is also apparent that many such reactions remain unexplained as to mechanism.

Although there has currently been limited investigation regarding the etiology or mechanisms underlying these HSRs, we believe that such an investigation is important for several reasons. First, there may be benefits to the patient from an evaluation of the cause of a reaction. These benefits might include desensitization to the offending drug so the patient could continue receiving a necessary agent, or even ruling out a true HSR in favor of a side effect or toxic reaction, so that the patient would not be given another drug of the same class with similar toxic effects. In addition, there are potential advantages in developing chemotherapeutic agents by evaluating HSRs, such as structurally altering an immunogenic compound to produce an equally effective, but less allergenic, drug. In an effort to gain these benefits, this section will attempt to encourage analysis of HSRs by providing an algorithm for use in the evaluation (Fig. 1), and by explaining their specialized immunologic tests required.

The first step in evaluating an adverse reaction to an antitumor agent involves deciding whether the reaction was a true hypersensitivity reaction, or more correctly, whether the reaction was caused by immunologic reactivity to the substance. This is

often the most difficult part of the analysis, because many toxic reactions can mimic immunologic reactivity through direct release of mediators. Several factors can help indicate whether a reaction might have an immunologic basis. One factor is that immunologic reactions usually require a prior exposure; one must be sensitized before becoming hypersensitized. This prior sensitization could occur during an earlier course of a drug, or may occur during the same period of administration if the agent is given over a long enough time (probably more than 1 wk). In addition, certain symptom complexes are more diagnostic of immunologically-mediated disorders. These include urticaria, angioedema, bronchospasm (wheezing), laryngospasm, cytopenias, arthritis, mucositis, vasculitic syndromes, and vesicular dermatitis [112]. A lack of any of these symptoms or an adverse reaction to an agent soon after the first dose makes it less likely that the patient had a true HSR.

Another factor that may help clarify the etiology of an adverse reaction in some individuals is their prior allergic history. This is especially true in questions of IgE-mediated reactions, in which patients who tend to form an IgE antibody response to drugs also tend to form them to other antigens, such as seasonal pollens [113]. Thus, suspicion that a patient might have had an IgE-mediated reaction to an antitumor agent may be heightened if the patient has a prior history of IgE-mediated, allergic disease.

While the aforementioned clues serve to direct the clinician to investigate the cause of a suspected HSR, the only way to determine the exact etiology is to evaluate the patient's specific immune reactivity to the suspected agent. In this respect, it is helpful to use the patient's symptoms as a guide to the appropriate laboratory evaluation of a possible HSR. The algorithm in Fig. 1 divides the evaluation of these reactions primarily along the lines of the four classes of HSRs, thus providing a rationale for choosing the specific immunologic tests needed. We will now discuss the evaluation and immunologic testing of these patients using this structure.

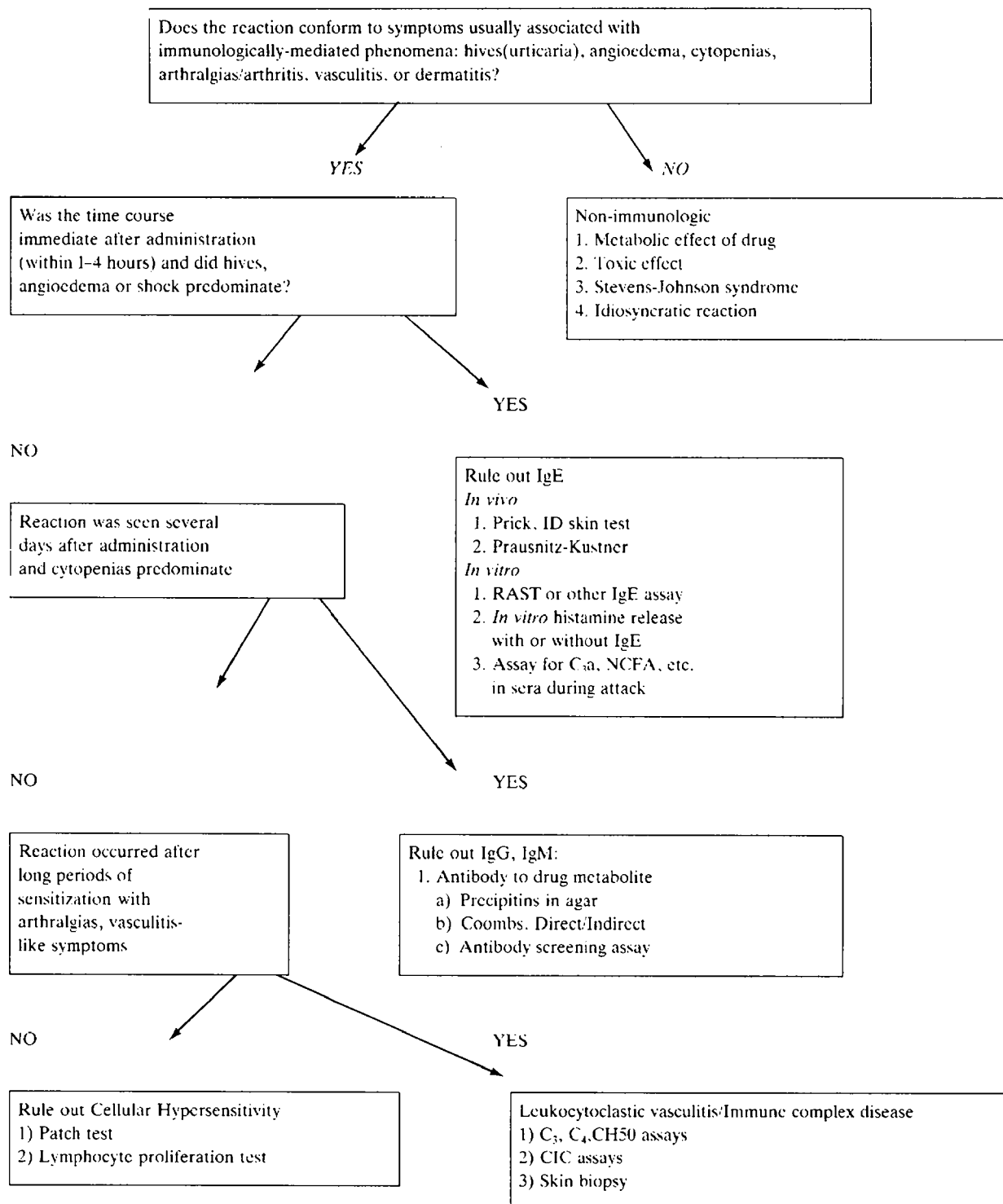


Fig. 1. Does the drugreaction conform to symptoms usually associated with immunologically-mediated phenomena: Adverse drug reaction. An algorithm for the evaluation of suspected HSRs.

Type I reactions

Type I reactions are those associated with immediate, or anaphylactic, symptoms. Patients usually display urticaria, angioedema, or bronchospasm, and can progress to cardiovascular collapse and shock. Type I reactions characteristically occur within 1 hr of challenge with an offending agent, but can occur up to 24 hr after exposure. If patients have these symptoms, their evaluation centers around the cause of Type I reactions: the interaction of sensitizing compound with specific IgE, which then causes the release of mediators from mast cells and basophils.

The most important tests for evaluating type I reactions are those that assay for antigen specific IgE. These generally fall into two types: bioassays, such as skin tests, and *in vitro* immunoassays, such as the RAST test. Skin testing remains the most sensitive assay for antigen-specific IgE and has the added advantages of being inexpensive and easy to perform [114]. A small amount of the offending agent is introduced by placing a drop on the skin and pricking through the drop, or by injecting a small amount of the material directly into the dermis. If antigen-specific IgE is present in the skin there will be a release of mediators from mast cells, causing vasodilation (a flare reaction) and edema (a wheal formation) at the site of the injection. Often serum from an affected patient can be injected into the skin of a control individual, thus sensitizing a small area of skin. Transfer skin testing (called Prausnitz-Kustner tests) can then be carried out on this area to confirm reactivity. However, antihistamines administered during chemotherapy may mask skin test reactivity, and the transfer of serum from patients with cancer to others is undesirable. In these cases, *in vitro* tests for IgE may be appropriate. These tests involve placing the suspected sensitizing material on a solid phase, such as a paper disk, and mixing in the patient's serum. Antigen-specific IgE bound to the disk is then detected by radiolabelled or enzyme-labelled antiserum to IgE. These tests are limited, however, in that the appropriate solid phase must be developed, since no commercial assay for any of the chemotherapeutic agents is available.

Another method of evaluating Type I reactions

is to test the patient for presence of the mast cell mediators that are thought to cause the reaction. Several of these mediators, including histamine and neutrophil chemotactic factor, are well characterized and are detectable by commercial assays. In addition, it has been well documented that histamine elevations occur in both the serum and urine of patients having allergic reactions [115]. A similar analysis can be done *in vitro* by adding the suspected agent to mononuclear cells in culture, both with and without the patient's serum, and measuring histamine release [114].

An example of the way that these tests might be used to evaluate a Type I reaction can be seen with the administration of L-asparaginase. A suspected adverse reaction with appropriate manifestations might be documented to be truly Type I due to elevated histamine levels in the serum or urine. However, since there have been reports that these reactions were due to anaphylatoxin generation from complement activation [9], some determination of L-asparaginase-specific IgE levels should be performed. Because of reports of false negative reactions in intradermal testing [8], it would be of value to develop an *in vitro* assay that might also be used to screen patients prospectively. These data would be valuable for patient care, because concomitant corticosteroid therapy might mitigate a complement-mediated reaction, but would not be expected to alter an IgE-mediated one.

Type II reactions

Type II reactions are the result of cell-surface target antigen interacting with IgM or IgG, with resulting destruction of the target. These reactions are less common with chemotherapeutic agents, because these drugs are small haptens that do not induce strong antibody responses. However, when these drugs are adsorbed on the surface of blood cells they can become more efficient immunogens, resulting in cytopenias. The development of an IgM response usually requires several days of exposure to the drug, and thus Type II reactions usually do not occur until 3 to 7 days after the initiation of therapy. This axiom must be tempered, however, by the fact that the more times an

individual is exposed to an antigen, the more rapidly the antibody response develops.

Any cell can adsorb a drug on its surface and act as a target in a Type II reaction, but the blood cells are most commonly involved. Screening tests for intravascular hemolysis are thus useful in diagnosing this problem, but the immunologic tests of choice for evaluation are the two Coombs' tests. The direct Coombs' test can determine whether there are immune elements on the surface of blood cells, while the indirect Coombs' test can be used to see if the patient's serum can sensitize cells [116]. The latter test is particularly helpful in the evaluation of drug-induced hemolysis, because it can be done both with and without pre-coating the cells with the drug.

In cases in which antibody-mediated cytotoxicity against solid organs (such as the lung) is suspected, the evaluation of Type II reactions is more difficult. Biopsy of the affected organ with subsequent immunofluorescence or immunoperoxidase staining for antibody and complement can be helpful in determining if there are immune elements involved. In addition, *in vitro* assays for drug-specific IgG or IgM can indicate whether there is an immune response to the chemotherapeutic agent.

An example of the evaluation of a suspected Type II reaction is seen in a patient who was reported to develop anemia after exposure to teniposide [117]. Because of the need to prove that the anemia was the result of hemolysis and not myelosuppression, testing was done that demonstrated intravascular hemolysis. The patient was then shown to have a positive direct Coombs' test that normalized after discontinuation of the drug, indicating that a drug-dependent antibody caused the hemolysis.

Type III reactions

Type III reactions are the result of antibody interacting with antigen, forming an immune complex. To form such a complex, both the antibody and the antigen must have more than one valence or binding site. All antibodies have this property, but, as implied in the previous section, most drugs are haptens and display only a single binding site.

Thus, for a Type III reaction to occur several molecules of drug have to be adsorbed either on a cell surface or to a protein to make a multivalent antigen. Moreover, since the soluble immune complexes that cause Type III reactions tend to form in *antigen* excess, these reactions usually occur after prolonged administration (at least 4 to 7 days) of large amounts of drug.

Type III reactions have diverse manifestations that are primarily related to the multiple effector mechanisms that immune complexes can activate. Complement activation is central to most of these processes, because immune complexes activate complement efficiently by means of the classical pathway. This can lead to anaphylotoxin production, mimicking Type I reactions, as well as the generation of molecules that attract inflammatory cells, causing local tissue damage. These phenomena can be localized in a single organ such as the kidney or liver, or they can cause generalized reactions such as anaphylactoid reactions or hypersensitivity vasculitis.

The evaluation of Type III reactions is complicated and revolves around assays for complement function and activation [114]. Despite the fact these assays are not 'drug specific' and thus provide only circumstantial evidence of a hypersensitivity reaction, generalized Type III reactions can often be detected with assays for circulating immune complexes, such as Clq and Raji cell assays. If Type I symptoms are present it might be of value to assay for C3a, a complement fragment that is an anaphylotoxin. It is also helpful to measure levels of complement components to determine if there is consumption of complement. Overall consumption can be measured by the CH₅₀ assay, and assays for C3 and C4 can demonstrate activation of the early part of the pathway. C4 levels can be particularly helpful in determining whether complement activation is due to immune complex formation or mediated by activation of the alternate pathway, since C4 is only consumed in classical pathway activation [118]. A biopsy of the involved tissue is often helpful in confirming a suspected case of hypersensitivity vasculitis because of the characteristic findings of 'nuclear dust' fragments in involved vessels [119]. A biopsy may also be helpful in localized disease or when systemic complement activation is not apparent.

An example of how one might evaluate a suspected Type III reaction is seen with the antitumor drug zinostatin. This agent has been associated with a pneumonitis suggestive of a localized immune complex (Arthus) disease [120]. Although there were characteristic findings compatible with vasculitic changes on lung biopsy, immunofluorescence staining of the tissue was negative for immune complexes. Unfortunately, this is often the case after inflammatory changes have occurred in the tissue for more than 72 hr, and immune complex disease is not necessarily ruled out [121]. Further testing for circulating immune complexes or complement activation might have resolved this question.

Type IV reactions

Type IV reactions are the result of cellular sensitization to an antigen with the generation of a cell-mediated cytotoxic response. This response can be mounted by T cells independent of B cell activity, so that specific antibody against the inciting drug is not commonly demonstrated. Instead, cytotoxic T cells destroy drug-coated target cells directly through cell-cell contact. This contact is initiated by specific receptors for the sensitizing drug and histocompatibility antigens on the surface of cytotoxic cells, after which the cytotoxic cells release compounds that lyse the target cells.

Clinical manifestations of Type IV reactions include vesicular dermatitis, stomatitis, and possibly organ-specific reactions including pneumonitis, interstitial nephritis, and dermatomyositis. The basis for the organ-specific disorders is still controversial, however, because it is difficult to demonstrate specific cellular sensitivity to a drug by any means other than contact dermatitis. As a result, the diagnosis of cellular hypersensitivity is most often made on a presumptive basis when the particular reaction resolves promptly (within 48 hr) after discontinuation of the suspected drug [122].

Despite the controversy over the immunologic basis of many of these reactions, there are several possible tests for evaluating suspected Type IV reactions. Patch testing with the drug is probably the most effective means of determining cellular

sensitization [122]. To perform this test the drug is coated on an occlusive patch, which is then placed on the skin for 48 hr. After removing the patch the skin under this site is examined for signs of inflammation which, if present, indicate sensitization. The major problem with this test using chemotherapeutic agents is that false positive reactions can be caused by direct drug toxicity to the epidermis. This can be resolved, however, by using appropriate concentrations of the agent, as well as by patch testing control subjects. *In vitro* testing for cellular sensitization involves adding dilutions of the suspect drug to isolated lymphocytes from the patient in tissue culture and then measuring lymphocyte proliferation in response to the drug [123]. Several methods can be used to quantify this proliferation, but the one most commonly used incorporates radiolabelled thymidine into the cellular DNA. This test is very sensitive, but it suffers from false negative reactions due to the toxic effects of the agents on the lymphocytes, which can directly inhibit lymphocyte proliferation.

The clearest case of a Type IV reaction to a chemotherapeutic agent is seen with topical mechlorethamine. This drug is applied topically to treat mycosis fungoides and causes a contact sensitization in a manner similar to Rhus ('poison ivy') dermatitis in 30% of patients treated [124]. Cellular sensitivity has been demonstrated through patch testing (but not by *in vitro* tests) using the drug. Sensitivity is also supported by the fact that patients were reportedly desensitized by small amounts of drug administered intravenously before topical therapy was initiated.

Conclusion

HSRs can be a major and life-threatening form of chemotherapy toxicity. Although the immunologic evaluation of these reactions is still very rudimentary, its performance may add significantly to the limited knowledge of the way that certain agents cause such reactions. While the value of immunologic testing is primarily in helping to decide whether to discontinue an agent due to a questionable HSR, such testing may supply enough information in certain situations (such as IgE-mediated

reactions) to allow therapy to be re-started after appropriate desensitization. Thus, the application of immunologic testing in suspected HSRs may improve both chemotherapy efficacy and patient care.

Key unanswered questions

The mechanisms of many HSRs secondary to antineoplastic agents have been poorly evaluated. Whenever such a reaction is observed, a thorough analysis (Fig. 1) may provide insight that would lead to either better control or prevention of HSRs. The evaluation of the type II reactions from elliptinium, with resultant modification of the drug administration schedule, is an example of what can be accomplished in this regard. An important determination is whether or not the reaction is immunologically or non-immunologically mediated. Another major question is whether the formulation product (e.g., Cremophor EL) is the cause. Alternative formulations may reduce the problem of HSRs. Analogues of agents to which a patient is sensitive frequently have little or no cross-reactivity. It is important to document instances both of cross-reactivity and a lack thereof, whenever analogue substitutions are made for a reactive patient.

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