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Review article

Hypersensitivity reactions to chemotherapy drugs

Antineoplastic therapy aims at completely eliminating all neoplastic cells, by either surgical, radiotherapeutic or pharmacological (administration of drugs) intervention. If this is not possible or feasible, the aim of therapy becomes palliative, that is, its purpose is to reduce the number of neoplastic cells, to improve the symptoms and, if possible, to prolong survival while maintaining an adequate quality of life. Neoplastic cells constitute a heterogeneous cellular population, with biochemical, morphological and immunological differences. Consequently, they evidence a widely varying sensitivity to antineoplastic drugs. Furthermore, not all the cells present in a given tumour are in the same phase in the cell cycle (generally, in the proliferative or in the rest phase). When a neoplasm is diagnosed, most of its cells have usually attained a phase of decelerated growth, because of vascularisation problems, of nutrient competitiveness problems, of lack of physical space, or of problems of other types. Many of the chemotherapeutic drugs are most effective on cells that are in their division process, and this means that, in principle, a large proportion of the neoplastic cells will be resistant to the effects of a given drug. Furthermore, the administration of one concrete antineoplastic drug will certainly eliminate the cell population that is sensitive to it, but it will also in the long run select the resistant population. Because of this, a well- and solidly established principle in antineoplastic chemotherapy is that multiple drugs must be used, preferably in a successive or phase-associated schedule, according to the kinetic and biochemical changes the tumoural cells undergo. Modern chemotherapy avails itself, further to the (truly) cytotoxic drugs, of further agents that are differentiation inducers, radiosensitising agents, biological response modifiers and/or agents capable of inducing hypoxia in the neoplastic clone cells. A classification of these agents according to their mechanism of action is presented in Table I.

The action of antineoplastic drugs is not selective for neoplastic cells, so that they have quite considerable side effects that are mainly evident in cell lines expressing higher growth and replication rates. Furthermore, antineoplastic drugs may evidence a degree of selective toxicity on particular organs, mainly the lungs, the liver, the kidneys and the nervous system structures. They may (and do) also induce derangements in the replication and processing mechanisms of the cells involved in immune responses, so that their use leads to a state of immune depression facilitating the development of bacterial, viral and fungal infections. In the long run they also cause other forms of toxicity, such as mutagenicity and carcinogenesis.

In order to circumvent and/or prevent some of these side effects, a number of other compounds are added to the properly antineoplastic drug therapy. Thus, myelodepression may be prevented or palliated with the administration of

Table I. General classification of antineoplastic drugs

1. FOLIC ACID ANALOGUES	B) Alkylsulfonates
Methotrexate	Busulfan
2. PYRIMIDINE BASE ANALOGUES	C) Nitrosoureas
A) Uracyl analogues	Chloroethylnitrosourea, carmustine, lomustine y semustine
5-fluorouracil, floxuridine, ftorafur	Streptozotocin, chlorozotocin
B) Cytosine analogues	D) Ethyleneamines and methylmelamines
Cytarabine, 5-azacytidine	Thio-TEPA, alternamine
3. PURINE BASE ANALOGUES	E) Atypical alkylating agents
6-mercaptopurine, 6-thioguanine	Procarbazine y dacarbazine
4. DRUGS BINDING TO TUBULIN	6. PLATINUM SALTS
A) <i>Vinca</i> alkaloids	<i>Cis</i> -platin, carboplatin
Vincristine, vinblastine, vindesine	7. ANTIBIOTICS
B) Epipodophyllotoxins	Bleomycins
Etoposide (VP-16), teniposide (VM-26)	Dactinomycin
C) Taxanes	Anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicina)
Docetaxel, paclitaxel	Mitoxanthrone
5. ALKYLATING AGENTS	Mitomycin C
A) Nitrogen mustards	8. OTHER DRUGS
Mechlorethamine	Hydroxyurea
Melphalan	Asparaginase
Chlorambucil	Amsacrine
Cyclophosphamide, iphosphamide	

Table II. Classification of chemotherapeutic drugs according to their skin toxicity

Non-aggressive cytostatics	Irritant cytostatics		Vesicant cytostatics	
Asparaginase	Bleomycin	Estramustine	Amsacrine	Mitomycin
Cytarabine	Carmustine	Etoposide	Actinomycin C	Vinblastine
Fludarabine	Carboplatin	Fluorouracyl	Daunorubicin	Vincristine
Gemcytabine	Cyclophosphamide	Mitoxanthrone	Doxorubicin	Vindesine
Iphosphamide	Cis-platin	Paclitaxel	Epirubicin	Vinorelbine
Melphalan	Dacarbazine	Teniposide	Idarubicin	
Methotrexate	Docetaxel		Mechlorethamine	

haemopoietic growth factors, blood transfusions, and bone marrow transplants. Powerful antiemetics are given in order to minimise the nausea and vomiting that are associated as a form of immediate toxicity to many antineoplastic drugs, particularly when such medication is given in successive cycles. Finally, analgesic/antalgic therapy is very important in the general management of patients with neoplastic diseases.

The assessment of allergic reactions to chemotherapeutic drugs represents a very significant challenge, and at the same time a highly intriguing area in the study of immediate-hypersensitivity drug reactions. In the first place, the mechanisms of immediate hypersensitivity reactions to

these drugs are not adequately known, for a number of reasons. On the one hand, these reactions are, with the exception of certain drugs as will be discussed later, fortunately rather scarce, so that studies with large numbers of patients are not possible. Further to this, the immunologic mechanisms that give rise to these reactions have not been adequately studied, and investigators oftentimes restrict themselves to the administration of preventive therapy based on corticosteroids and antihistamines, or even to the withdrawal of the causative drug, even though the drug has been in some cases reintroduced, at times without any previous studies and with quite divergent results. In the second place, patients receiving chemotherapy are normally given, as previously stated, multiple associated or combined chemotherapeutic agents, often with the addition of adjuvant therapy comprising growth factors, antiemetics and analgesics. If the patient evidences an infectious process he/she may well be also receiving antimicrobial therapy, usually with several combined antimicrobials at the same time. All these drugs are at least in theory able to cause an allergic reaction, so that it is difficult to assess which of the various drugs given is actually responsible for the allergic reaction observed. A further problem is that adequate *in vivo* methods are not available, as many of the chemotherapeutics are irritant or vesicant (Table II); it is also difficult to have adequate controls, as

Table III. Skin tests with chemotherapeutic drugs

Drug	Skin Test	Concentration	Controls	Reference
Cis-platin	Prick ID	0,1 mg/ml 10 ⁻³ -10 ⁻³ mg/ml	Yes	10
Cis-platin and carboplatin	Prick ID	1-10 ³ mg/ml 1-10 ³ mg/ml	Yes	20
Carboplatin	Prick ID	2,7.10 ⁻³ a 10 mg/ml 2,7.10 ⁻³ mg/ml	Yes	27
Carboplatin	ID	50 mg/ml	No	19
Carboplatin	Prick ID	50 mg/ml 50 mg/ml	No	23
Cyclophosphamide	Prick	1-10 mg/ml	Yes	58
4-Hydroperoxy-cyclophosphamide	ID	1-10 mg/ml		
Mustard-phosphamide				
Cyclophosphamide	ID	1-10 mg/ml	No	51
4-Hydroxyperoxy-CP				
Mustard-phosphoramidate				
Mustard-nor- nitrogen Isophosphamide				
Mustard-isophosphoramidate				
Cyclophosphamide	ID	10 mg/ml	Yes*	57
4-Hydroxyperoxy-CP				
4-Keto-cyclophosphamide				
Mustard-phosphoramidate Phosphamide				
Cytarabine	Prick, ID	4 mg/ml	No	90
Epirubicin	Patch	0,1% aqueous	Not stated	174
5-Fluorouracyl	Prick	0,001-1 mg/ml	Yes	84
L-asparaginase	ID	5-50 U/ml	No	111
Methotrexate	Prick	10 mg/ml	Yes	189
Mitomycin C	Patch	0,06; 0,2 y 0,6% aq. 0,06 y 0,2% vaseline	Yes	183
Mitomycin C	Patch	0,001-0,01%	Yes	185
Methotrexate	ID	25/mg/ml	NO	
Paclitaxel	ID	50 mg/ml	NO	19

ID = intradermal test; CP = cyclophosphamide; *two of the controls had positive skin tests with mustard-phosphoramidate.

the very nature of these compounds precludes their administration to healthy control subjects. As for *in vitro* tests, the problem is similar to that with many other drugs: the lack of adequate reagents. In order to establish a definite certainty diagnosis, it is sometimes necessary to carry out an exposure challenge test, with all the risks this involves in patients who, additionally, may evidence a poor general condition or severe involvement of vital organs and who in many cases will also be of advanced age. Also, when hypersensitivity to one particular chemotherapeutic drug is

Table IV. Recommendations for the prevention of hypersensitivity reactions to chemotherapeutic drugs

Prevention of hypersensitivity reactions caused by antineoplastic drugs (from Weiss³, modified)

Premedication

Dexamethasone 20 mg p.o. 12 and 6 h before therapy, and 20 mg i.v. immediately before therapy
 Dexchlorphenyramine 6 mg p.o. or 5 mg i.v., with the same schedule as for dexamethasone
 Consider ephedrine sulfate 25 mg p.o. 1 hour before therapy unless the patient has unstable angina pectoris or is hypertensive
 Careful suppression (whenever possible) of any β -blocking medication that might potentiate a reaction or hamper its management

Particular measures during therapy administration

Maintain a venous access
 Arterial blood pressure monitoring (if available)
 Ensure that epinephrine and diphenhydramine for parenteral administration are immediately available
 Keep the patient under observation for two hours after the administration of the antineoplastic drug is finished

diagnosed it is often not possible to give an alternative therapy for an underlying condition which, if not treated, will speedily put an end to the patient's life. In the third place, the chemotherapeutic drugs themselves, or the associated immunomodulatory drugs, may cause considerable changes in the immune system that may induce either an increase or potentiation of hypersensitivity reactions or important changes in the immune response mechanisms of the host, which in turn may render the assessment of the eventual reactions even more difficult. There have been reports of rashes during the recovery phase of the leukocyte counts, which have been attributed either to the recovery of the cell counts per se (leukocyte recovery rashes) or to an expression of a drug reaction that becomes manifest only when the immunocompetent cell counts have achieved a sufficient level.

We shall here review in detail the immediate hypersensitivity reactions to the main chemotherapeutics. Immunomodulating or other adjuvant or complementary drugs shall not be discussed, as this would mean an excessively exhaustive examination. Each drug will be shortly described, together with its mechanism, of action, its principal indications and its reported hypersensitivity reactions. Particular emphasis will be made on the suggested hypersensitivity mechanisms, on the diagnostic tests and

on cross-reactivity when studies considering this aspect are available. Table III summarises those studies in which skin tests with antineoplastic drugs have been performed, together with the test dosages used. Table IV shows the general recommendations units on the use and application of premedication in Oncology.

Cis-PLATIN AND CARBOPLATIN

Cis-platin acts preferently on the DNA bases and especially on the nitrogen atom in position 7 in guanine, due to its great nucleophyllia. Its behaviour is similar to that of alkylating agents, and it further produces bridging between the two DNA strands and even between guanine molecules within the same strand, and also between DNA and proteins. The overall result is a strong inhibition of DNA synthesis.

Its main toxicity involves the kidney, and this can be prevented in part through abundant hydration and osmotic diuresis. It also causes severe nausea and vomiting and is furthermore ototoxic and an inductor of myelodepression and haemolysis.

It is mainly used in testicular and ovarian carcinoma in combination with other products. It has also been used in small-cell carcinoma of the lung, in gastric carcinoma, in choriocarcinoma and in urinary bladder malignancy.

Hypersensitivity. There have been reports of hypersensitivity reactions to cis-platin since it first entered clinical use in the early '70s. The incidence of reactions ranges between 1 and 20%, depending on its being used as monotherapy or in combination with other chemotherapeutic drugs¹. Cheng *et al.*² reported seven cases of allergic reactions to cis-platin among 50 patients (14%), without specifying the characteristics of the reactions. However, the data on the incidence of reactions are not reliable, as it was much higher at the beginning of its clinical application, when more than six therapy courses were usually given, than at present when three or four courses are not usually exceeded and diphenhydramine and/or dexamethasone are given for prevention of the emesis this drug induces³. Several cases of immediate hypersensitivity reactions to cis-platin have been reported, usually after several therapy courses⁴⁻⁸, although the mechanism has not yet been fully clarified and both immediate-hypersensitivity and non-immunologic mechanisms have been postulated. One report describes loss of consciousness and hypotension after the administration of five therapy courses with cis-pla-

tin⁹. In this case a positive intradermal test with cis-dichlorodiamino-platin (DDP, 1/10,000) was elicited, with negative controls, as well as a positive histamine release test with 1/1000 DDP. Desensitisation to DDP was also successfully carried out, with hydroxyzine and methyl-prednisolone premedication. Goldberg *et al.*¹⁰ report two cases of cis-platin anaphylaxis occurring after several therapy courses; later administration of the drug with premedication was unable to prevent reactions. In both cases the patients had positive intradermal tests with 0.1 mg/ml cis-platin. On the other hand, immediate hypersensitivity reactions to platin salts have been demonstrated in industrial workers^{11,12}, as well as the presence of specific IgE¹³. However, cases have also been also reported with suggestive symptoms and negative skin tests, histamine release and lymphocyte stimulation tests, with tolerance of the drug after diphenhydramine premedication⁷.

The intravesical use of cis-platin appears to be associated with a high incidence of reactions. In at least two studies, an incidence ranging from 10 and 25% of all treated patients has been reported^{14,15}. In all these cases the reactions occurred after at least eight therapy courses. It is suggested that this high incidence of reactions may be due not only to the high number of exposures but also to the fact that in the intravesical administration of cis-platin antiemetic medication is not routinely used³. One case of anaphylactic reaction after intraperitoneal administration of cis-platin has been recently reported¹⁶, and also another one after administration of carboplatin by this same route¹⁷.

Other platin compounds have also been used. Reactions to carboplatin occur in less than 8% of the patients; they appear to occur in successive therapy courses and are exceptional in the first one^{5,6,18-20}, suggesting a hypersensitivity mechanism rather than a histamine-release one. However, Morgan *et al.*²¹ describe 14 patients with hypersensitivity reactions (not specified) who later tolerated carboplatin administration some of them with chlorpheniramine premedication. Even so, the authors themselves recognise that they did not administer carboplatin to one patient with anaphylactic shock. Chang *et al.*²² reported five children with hypersensitivity reactions to carboplatin, always after a number of therapy courses. Reintroduction was attempted in four of them, but the reactions reappeared even under premedication. Sood *et al.*¹⁹ describe one case of anaphylactic shock after 14 courses of carboplatin chemotherapy. This patient had a positive intradermal test with carboplatin (50 µg/ml) and a negative one

with paclitaxel (also a component of the therapy courses, and later tolerated) and with mannitol, a constituent of the commercial preparations of cis-platin and carboplatin. Broome *et al.*²³ report two cases of carboplatin desensitisation in two children who had developed immediate hypersensitivity reactions after the administration of several therapy courses. The skin tests were negative (50 µg/ml), and a desensitisation protocol was instituted prior to each carboplatin infusion, with good tolerance in one case and with skin reactions in the other one, which were controlled with antihistamine premedication. Kook *et al.*²⁴ describe one case of life-threatening reaction after the administration of carboplatin in the preparation for autologous bone marrow transplantation. One case of anaphylactic death has also been reported in relation to the administration of carboplatin despite the use of corticosteroid and antihistamine premedication²⁵.

Five cases of anaphylactic reactions have recently been reported with oxalyplatin²⁶, a new platin compound with activity in colorectal cancer.

Cross reactivity. The existence of cross-reactivity between the various platin compounds is not well established. Windom *et al.*²⁰ describe the case of a female patient who developed anaphylactic shock after the second course of carboplatin therapy (in the first one she had evidenced palmar pruritus) and who had previously tolerated several cis-platin courses. The intradermal skin tests were positive with both compounds, but the authors could not demonstrate specific IgE by RAST. They however instituted a desensitisation protocol that the patient tolerates with only mild pruritus. In the case of anaphylactic shock reported by Sood *et al.*¹⁹, the patient had previously tolerated several therapy courses with cis-platin, and skin tests with this agent were not performed. Planner *et al.*¹⁸ describe two patients who developed hypersensitivity reactions to carboplatin after having tolerated several therapy courses with cis-platin; they had also received several therapy courses with carboplatin previously. Weidmann *et al.*²⁷, however, report two cases of carboplatin hypersensitivity after having tolerated a first therapy course with carboplatin and etoposide, occurring upon reintroduction of the drug because of tumour progression. In one of the cases carboplatin was reintroduced with prednisone (150 mg) and antihistamine premedication, and reactions occurred in two later therapy courses. Nevertheless, both patients tolerated later therapy courses with carboplatin without incidences.

There have also been reports of cases of acral erythema induced by cis-platin²⁸.

ALKYLATING AGENTS

Alkylating agents act by creating covalent bonds between their alkyl groups and a number of nucleophilic molecules present in the cells. Some of them act through a highly reactive intermediate group. They are active in all phases of the cell cycle, but preferentially during the replication process.

Busulfan

This agent is characterised by its specific action on the bone marrow, with relative selectivity for the granulocytic series. It is mainly used in the treatment of chronic myelocytic leukaemia. The most constant adverse reactions derive from the induced myelodepression; further adverse events are nausea, vomiting, pulmonary fibrosis, alopecia, azoospermia, amenorrhoea, chromosomal alterations and teratogenicity.

Hypersensitivity. Few reports of reactions have been published. There has been one report of erythema multiformis²⁹ and two of urticaria³⁰. A pruriginous, erythematous maculo-papular rash has been reported in two patients receiving busulfan and allopurinol at the same time; the rash reverted upon discontinuation of the two drugs, but then reappeared when therapy with busulfan alone was reintroduced³¹.

Melphalan

Mainly used in combination with other drugs in the therapy of myeloma, melphalan was used in the past in ovarian cancer. Its most frequent adverse effects are myelotoxicity (mainly affecting the thrombocytic series), lung involvement and carcinogenesis.

Hypersensitivity. Cutaneous reactions are not frequent with this agent. In two large series, reactions of this type have been reported in 2 out of 48 patients in one³² and in 1 out of 64 in the other³³. Pruritus, urticaria, angioedema, vasculitis, maculo-papular rashes and anaphylaxis have also been reported³⁴⁻³⁶. One case has been reported of a patient developing pruritus and a diffuse erythematous-papular rash after five administrations of the drug³⁴; six weeks later a single dose of the agent was administered and elicited a more severe reaction with paresthesias in the hands, dizziness, pruritus, hypotension, abdominal cramps and slight dyspnoea, which again occurred upon the administration of mel-

phalan 30 days later. In one study of 425 patients receiving intravenous (i.v.) melphalan³⁵, reactions were reported in ten cases (2.4%). These reactions ranged from oedema and generalised rashes to anaphylaxis, and occurred after a median period of 222 days of therapy and after a median cumulative dose of 185 mg. However, in that same report³⁵, in 294 patients receiving only oral melphalan only one reaction was observed. However, there has also been one report of an allergic reaction to i.v. melphalan with later tolerance to the oral drug³⁷. It is not clear why the intravenous route is apparently more allergenic than the oral one. An allergic reaction to the intravenous excipient does not appear to be involved, as melphalan is dissolved in 10% ethanol and then diluted in normal saline; the reaction also does not seem to be related to variable bioavailability of the orally administered drug, although this in fact occurs. As for the mechanism involved, this is still unknown; the fact that all the reported reactions occurred after previous exposure to melphalan suggests a possibly IgE-mediated hypersensitivity mechanism. One case of melphalan-associated vasculitis has also been reported³⁶.

Chlorambucil

This agent is mainly used for chronic lymphocytic leukaemia and for Waldenström's macroglobulinaemia. It may also be useful in Hodgkin's disease and in other lymphomas. Chlorambucil causes moderate, gradual and reversible myelosuppression; it can also induce gonadal atrophy and carcinogenesis.

Hypersensitivity. There are few reported cases of hypersensitivity reactions attributed to chlorambucil³⁸. Urticarial and angioedematous reactions have been described^{39,40}, as well as generalised erythematous rashes⁴¹ and even toxic epidermal necrolysis^{41,42}, some of them confirmed by skin patch test and biopsy. There is also one published case of hyperpyrexia, chills and haemolysis episodes, which reappeared upon reintroduction of the drug and in which the causative role of chlorambucil was demonstrated by an *in vitro* assay⁴³. Delayed hypersensitivity reactions have also been reported, manifesting as fever, tiredness, myalgia, pruritus and erythema in the second course of chlorambucil and prednisone therapy, and again occurring during the third course as myalgia, generalised erythrodermia and oedema and exfoliation of the face and hands; a patch test with chlorambucil was positive, with biopsic confirmation⁴⁴.

Thio-TEPA

This alkylating agent is highly lipophilic and penetrates readily and rapidly into the central nervous system. In clinical practice, however, it has been used almost exclusively in the therapy of superficial cancer of the urinary bladder, in intracavitary application. Its most noted toxicity is myelodepression, even when administered intravesically.

Hypersensitivity. There are very few reports of hypersensitivity reactions to thio-TEPA. Lee and Sharifi⁴⁵ have reported one case of generalised pruritus after intravesical administration of the drug, in a patient who also developed a reaction to intravesical doxorubicin.

Carmustine

This drug belongs to the nitrosourea group. These compounds decompose spontaneously into further products that are responsible for their cytotoxic action: chloroethyl-diazonium and chloroethyl-carbonium ions, and isocyanate. The main toxic effect is delayed myelotoxicity affecting predominantly the leukocytic and thrombocytic series. They also frequently cause nausea and vomiting, and may induce renal toxicity, irreversible pulmonary fibrosis, reversible hepatic damage, local irritation and neurologic reactions. They are mainly used in the therapy of Hodgkin's disease and of other lymphomas and myelomas, in combination with other drugs, or as alternative drugs in the therapy of leukaemias with meningeal involvement and in primary or metastatic tumours of the brain.

Hypersensitivity. Practically no hypersensitivity reactions have been described. It has been reported that rapid i.v. administration of carmustine may induce facial rubor and conjunctival reaction, appearing within the first two hours and lasting for up to four hours⁴⁶. Some isolated cases of maculo-papular reaction have also been reported⁴⁷.

Cyclophosphamide and iphosphamide

These are bi-functional alkylating agents. Iphosphamide is a structural analogue of cyclophosphamide, from which it differs only in the location of the chloroethyl groups. Both are prodrugs which are transformed in the organism into products with alkylant cytotoxic activity. The metabolites of cyclophosphamide are known; the parent drug is first transformed into 4-hydroxy-cyclophosphamide, which is in turn transformed into alphasphamide. The

latter is transformed by enzymatic oxidation into carboxyphosphamide and then into nor-nitrogen mustard, or by spontaneous oxidation into mustard-phosphoramidate and acrolein. The latter accumulates in the urinary bladder and is the cause of the non-bacterial haemorrhagic cystitis, which can be prevented through mesna administration. The main toxicity is nausea and vomiting, together with myelosuppression that is more readily reversible than with other alkylating drugs. They also induce alopecia, suppression of antidiuretic hormone (ADH) secretion and teratogenesis. Cyclophosphamide may also induce pulmonary infiltrates and bladder cancer (with prolonged administration), and iphosphamide may induce an encephalopathic condition.

When used as an antineoplastic agent, cyclophosphamide has a wide spectrum of action; it is easy to administer, and the dosage range is extensive. It is mainly used in combination with other drugs in Hodgkin's disease, lymphomas, acute childhood lymphoblastic leukaemia and Burkitt's disease, but also in many other neoplasms. Iphosphamide is used in monotherapy or in associations in sarcomas and in lung, ovarian, testicular, neck and breast tumours.

Hypersensitivity. Hypersensitivity reactions have been reported ranging from urticaria, angioedema or both, to anaphylaxis⁴⁸⁻⁵³, and there have been reports of cases of cutaneous vasculitis⁵⁴. Cyclophosphamide reactions may be immediate^{48,50,52} or appear after several hours^{49,51,53}. There are cases reported with immediate onset with a positive Prausnitz-Küstner passive transfer test⁵⁵, thus confirming that the causative antibody was of the IgE class, and also cases with a positive skin test with cyclophosphamide^{50,56}. In the late reactions, positive skin tests have been elicited to a metabolite of the drug⁵¹. There is also one reported case with immediate and late reaction and with positive skin tests with cyclophosphamide, 4-hydroxyperoxy-cyclophosphamide and mustard-phosphoramidate⁵⁷. Popescu *et al.*⁵⁸ have recently reported five cases of hypersensitivity reactions to cyclophosphamide; in four of them the reaction had been of the delayed type (8-16 hours after the administration of the drug), while the fifth patient evidenced her skin reaction ten days after administration, in two consecutive therapy courses. All five cases had immediate cutaneous response to cyclophosphamide metabolites (mustard-phosphoramidate or 5-hydroxyperoxy-cyclophosphamide), but not to the parent drug. The same tests were negative in four control subjects who had tolerated cyclophosphamide without any reaction. The first of the five patients, furthermore, also had a posi-

ve skin test with iphosphamide.

In some cases, the reactions may have been due to the mesna that is administered concomitantly⁵⁹⁻⁶¹.

Procarbazine

This is a synthetic antineoplastic drug with a powerful monoamine oxidase-inhibiting effect. It inhibits the incorporation of precursors into DNA, and can also inhibit protein synthesis and RNA through methylation. Its fundamental toxicity is haematological, together with nausea, vomiting, liver dysfunction and neurologic effects.

It is mainly used in advanced Hodgkin's disease and also in other lymphomas, in bronchogenic carcinoma and in cerebral tumours.

Hypersensitivity. Procarbazine is known to induce immediate hypersensitivity reactions. Skin manifestations comprise maculo-papular exanthema and urticaria, although toxic epidermal necrolysis may also occur⁶². In one reported series, 44 patients with Hodgkin's disease and 23 with non-Hodgkin lymphoma treated with a MOPP-type chemotherapy protocol were studied⁶³; four patients with Hodgkin's disease and eight with non-Hodgkin lymphoma developed maculo-papular exanthema. This frequency rate is higher than that expected from other literature reports. Complement activation has been described in some cases as the pathogenetic mechanism in procarbazine-induced reactions⁶⁴.

This drug can probably induce type III reactions (allergic alveolitis)⁶⁵. In some cases it is associated to peripheral blood eosinophilia, and in other cases interstitial infiltrates of eosinophils, lymphocytes, plasma cells and histiocytes, and sometimes granulomas, are detected in the lung biopsy. This type of reaction may also be associated to cutaneous exanthema and arthralgia^{66,67}.

There is no way of preventing these reactions. A slightly higher rate of hypersensitivity reactions to procarbazine has been observed in the treatment of cerebral tumours, such as gliomas⁶⁸. Multiple defects in the cell-mediated immune system have been observed in glioma patients, and this might explain their greater predisposition to drug hypersensitivity. An association has also been observed between administration of anticonvulsants and hypersensitivity reactions to procarbazine⁶⁹; it is suggested that phenobarbital may potentiate the oxidation of procarbazine to reactive intermediate metabolites, and this would explain the higher incidence of hypersensitivity reactions to procarbazine in these cases.

Hypersensitivity to this drug is rarely reported in the therapy of Hodgkin's disease⁶⁸.

Isolated cases of procarbazine-induced fixed drug eruption have also been reported⁷⁰.

Dacarbazine

This drug, also known as DTIC, is 5-(3,3-dimethyl-1,2,4-triazene)-imidazole-4-carboxamide. It is a non-cell-cycle-specific antineoplastic agent that functions as an alkylating drug after activation in the liver. Haematologic toxicity is its main toxic effect, followed by nausea and vomiting.

It is mainly used in metastatic malignant melanoma, and also in refractory Hodgkin's disease and in soft-tissue sarcomas.

Hypersensitivity. This is the only antineoplastic agent to commonly cause photosensitisation. The cutaneous manifestations are pruritus, erythema and oedema. The lesions appear only upon exposure to light and may easily be prevented by wearing protective clothing and avoiding direct sunlight for a few hours after the administration of the drug^{71,72}.

Dacarbazine has also been associated to liver toxicity elicited through an allergic mechanism⁷³. Necropsy findings reveal massive liver necrosis with thrombi in the small hepatic veins and vasculitis with lymphocytic and eosinophilic infiltration⁷⁴. This Budd-Chiari-like syndrome usually occurs during the second dacarbazine course and is associated to peripheral blood eosinophilia⁷⁵. This form of toxicity is rare.

One case of dacarbazine anaphylaxis has also been published⁷⁶.

Cross reactivity between alkylating agents. The existence of cross reactivity between the various alkylating agents has not been fully clarified. Cases have been reported in which the patients perfectly tolerated another alkylating agent, while still others have been published with reaction occurring against two different drugs of this group. Krutchik *et al.*⁵³ have reported one female patient who developed pruritus and urticaria several hours after the administration of cyclophosphamide; this drug was then discontinued and chlorambucil used in substitution, with full tolerance. Kim *et al.*⁵¹ described one case with a delayed cyclophosphamide reaction who had positive skin tests with its metabolite mustard-phosphoramidate, but negative ones with cyclophosphamide and with a structurally very similar drug, isophosphamide, which the patient then tolerated on i.v. administration. On the other hand, Kritha-

rides *et al.*⁴⁹ reported one patient who had an urticarial reaction with cyclophosphamide and again with chlorambucil. Manigand *et al.*⁷⁷ described one case of urticaria in a patient with IgA myeloma in relation to the administration of melphalan, which again occurred after cyclophosphamide. In the study by Popescu *et al.*⁵⁸, one of the patients had positive skin tests with mustard-phosphoramidate and iphosphamide, while in the other four patients the skin tests were negative. In the case of reactions induced by chlorambucil, another alkylating agent has generally been tolerated^{41,44,53}, although there are isolated cases reported of cross reactivity between cyclophosphamide and chlorambucil⁴⁹.

In summary, the cross reactivity between different alkylating agents is still unclear. There may be some risk in certain cases when substituting one agent for another one that has caused a reaction, so that caution and utmost care are required in these cases.

FLUOROURACYL

This is an analogue of uracil that incorporates a fluorine atom instead of a hydrogen atom in position 5. Its action derives on the one hand from the inhibition of thymidylate synthetase, thus depleting the cells of d-TMP, a nucleotide that is indispensable in DNA synthesis, and on the other hand from its incorporation into RNA, which is progressive and dose- and exposure time-dependent, thus interfering in the processing and actions of RNA.

Its main toxicity manifests itself in the gastrointestinal tract (nausea, vomiting, stomatitis and ulcerations) and in the bone marrow (predominantly through leukopenia). It induces less myelosuppression if administered as an i.v. infusion than with bolus administration. 5-Fluorouracil may also induce alopecia, conjunctivitis and acute neurological syndromes.

This drug is fundamentally used in adenocarcinomas of the digestive tract and of the breast, and less effectively in hepatomas and in carcinomas of the ovary, bladder, uterine cervix, prostate and oropharynx. In topical administration it is used for psoriasis and for premalignant keratotic skin lesions.

Hypersensitivity. A rather high number of patients may evidence cutaneous lesions in the form of maculopapular rash in the trunk and limbs⁷⁸. A frequent toxic manifestation with 5-fluorouracil is the development of palmo-plantar dermatitis, similar to the one triggered by

cytarabine, which may sometimes be bothersome enough as to become dose-limiting³. It begins with palmo-plantar paresthesias and progresses to erythema and oedema, with desquamation in 33% of the cases⁷⁹. Although it was initially thought to be due to prolonged infusion of 5-fluorouracyl⁸⁰, it was later seen to occur even though the doses were administered as a bolus⁷⁹. This manifestation has improved in some series with pyridoxine administration⁸¹, suggesting a toxic mechanism rather than one of hypersensitivity. Further skin manifestations include erythema, desquamation and scabbing, which occurred in five out of a series of 155 patients⁷⁸. One episode of angioedema has also been reported, which could not be prevented in spite of premedication with oral prednisone and diphenhydramine⁸². A report has also been published of an anaphylactoid reaction in a 60 year-old male after the tenth intravenous dose of the drug⁸³. There has also been one report of an anaphylactic reaction in a female patient, with a positive prick test with 5-fluorouracyl; the patient could be desensitised using an i.v. protocol with sequential increases of the infusion rates and drug concentrations, and she then tolerated 20 later courses after repetition of the same desensitisation protocol⁸⁴.

Topical administration of the drug may induce contact dermatitis reactions⁸⁵. One case of pustular contact dermatitis has also been described, with rosacea-like sequelae⁸⁶.

CYTARABINE

Cytarabine (or cytosine arabinoside, or ara-C) is a pyrimidine base analogue, and more precisely a deoxy-cytidine one. It enters the cells via a transport mechanism and transforms into the active product, ara-CTP. Its fundamental action is that of competitive and reversible inhibition of α -DNA polymerase. It also becomes incorporated to DNA and induces greater susceptibility to degradation and to the occurrence of abnormal replications and recombinations. Its greatest effect occurs during phase S of the cell cycle, and its activity is thus greater during the recovery periods after the exposure of the cells to some other cytotoxic drug. Its main toxicity is myelosuppression, particularly of the granulocytic series, and gastrointestinal toxicity manifestations; it may also induce reversible liver dysfunction.

It is used in the therapy of leukaemias (particularly acute myeloblastic leukaemia), in non-Hodgkin lympho-

mas and, given intrathecally, in leukaemic or carcinomatous meningeal infiltrations.

Hypersensitivity. Immediate hypersensitivity reactions to cytarabine are infrequent but they are highly interesting for the Allergologist, as the existence of specific IgE antibodies has been demonstrated. Rassiga *et al.*⁸⁷ described the case of a patient who developed an anaphylaxis episode while receiving cytarabine, and in whom the intradermal skin tests with cytarabine and the passive cutaneous anaphylaxis test were positive. Successful desensitisation was also achieved. Some authors have demonstrated histamine release in a hypersensitivity reaction induced by cytarabine, and postulated an IgE-mediated mechanism⁸⁸. Berkowitz *et al.*⁸⁹ demonstrated, using ELISA, the existence of specific IgE antibodies in one case of anaphylactic shock induced by cytarabine. In Spain, Blanca *et al.*⁹⁰ have reported the case of a nine-year-old girl who had evidenced three anaphylaxis episodes in relation to the use of cytarabine, and who three years later again required therapy with the drug. Skin tests with cytarabine were performed at this time with negative results, with tolerance to the drug under controlled administration. However, when the skin tests were repeated 14 days later they had become positive, suggesting resensitisation after reintroduction of the drug.

Other types of skin reactions were relatively infrequent until high doses of cytarabine began being used. Castleberry *et al.*⁹¹ described the cytarabine syndrome, comprising high fever, chills, sudoration, myalgia, arthralgia, conjunctivitis and a micropapular rash after protracted cytarabine administration. This syndrome may be prevented with corticosteroid administration, representing an alternative to therapy discontinuation. Hypotension to a degree close to shock has been reported in some cases⁹²; in some of them, the possibility of an immunologic delayed-hypersensitivity underlying mechanism has been investigated⁹², although the most likely explanation might lie in the association of a number of cytarabine-induced toxicities³.

Another form of delayed reaction to ara-C is palmo-plantar erythema^{93,94}, characterised by intense, often painful erythema of the palms and soles progressing to vesiculation and desquamation. This is often preceded by dyesthesias. On occasion, this manifestation involves only the ear⁹⁵. The phenomenon appears after about six days of ara-C administration and appears to be dependent on the duration of therapy⁹⁴. A similar manifestation has also been observed with other chemotherapeutic drugs (hydroxyurea, cyclophosphamide, 6-mercaptopurine, and others)^{3,96}. It has

also been occasionally reported in patients with leukaemia who had as yet received no treatment⁹⁷. The mechanism is unknown, but a toxic origin is postulated. Biopsies disclose vacuolar degeneration of the basal cells of the epidermis, dyskeratosis, and a diffuse leukocyte infiltration in the upper dermis⁹⁴. The evolution is usually to healing with no sequelae, and the patients may again receive ara-C⁹⁸. In some cases it has been reported that a short course of corticosteroids has rapidly resolved the problem, and even that prophylactic steroid administration has minimised later recurrences⁹⁹.

Finally, a form of dermatosis with marked neutrophil accumulation around the sweat glands may occur; this particular manifestation has been termed neutrophilic eccrine hidradenitis. The skin has a dense, erythematous aspect, and indurated plaques are observed in the trunk and the proximal areas of the limbs^{100,101}. This has also been described in patients receiving other chemotherapeutic drugs¹⁰¹ and, although the mechanism is still unknown, it is thought to represent a toxic phenomenon. This particular form of reaction is in any case quite infrequent.

One case of toxic epidermal necrolysis in relation to cytarabine has been recently reported¹⁰².

L-ASPARAGINASE

The enzyme L-asparaginase hydrolyses asparagine into aspartic acid and ammoniac. L-asparagine is a non-essential aminoacid that is synthesised by the cells through the action of the enzyme L-asparagine-synthetase. Some cells, such as those of acute lymphoblastic leukaemia, lack this synthetic pathway and thus depend on exogenous L-asparagine. L-asparaginase therapy reduces the plasma levels of the aminoacid and thus interferes in protein synthesis.

This therapy has only slight effects on the bone marrow, the epithelia and the mucosae. It induces frequent immediate reactions manifesting as nausea, vomiting, chills and fever: some of these reactions are a consequence of the inhibition of the synthesis of certain proteins. L-asparagine may also induce neurologic reactions, liver dysfunction and haemorrhagic pancreatitis. It is particularly useful in acute lymphoblastic leukaemia with resistance to other chemotherapeutic drugs.

Hypersensitivity. L-asparaginase is the antineoplastic agent with the greatest risk of inducing immediate hypersensitivity reactions. It is estimated that reactions may oc-

cur in 5 to 35% of the cases^{103,104}, although in extensive series the incidence is estimated to be 15% among treated patients¹⁰⁵, with a 5-8% risk for each dose that increases up to 33% after the fourth one^{103,105}. Life-threatening anaphylactic reactions occur in less than 10% of the cases, and reactions with fatal outcome are rare¹⁰⁵. The symptoms are characteristic for an immediate hypersensitivity reaction, and usually occur within the first hour after administration. Intravenous administration increases the risk of reactions¹⁰⁶, so that the intramuscular route is recommended. The incidence of reactions is increased in those patients not receiving concomitant therapy with prednisone-vincristine¹⁰⁵; nevertheless, high doses of corticosteroids are not completely protective⁵⁴. Further risk factors are an interval between therapy courses in excess of one month or the administration of the drug at weekly intervals¹⁰⁵, as well as a past history of exposure to L-asparaginase even if that previous exposure had not triggered any reaction.

The mechanism underlying the reactions has not been clearly established. L-asparaginase is a polypeptide of bacterial origin (*Escherichia coli*), so that it is not surprising that allergic reactions to the drug may arise. As the patients develop reactions fundamentally after several therapy courses, it has been postulated that the mechanism might be through production of IgE antibodies. In this context, Khan and Hill¹⁰⁷ demonstrated, by means of skin tests and of the Prausnitz-Küstner reaction, the involvement of IgE at least in some cases. However, other authors¹⁰⁸ have detected complement activation, and suggested an immune complex formation and anaphylotoxin-release mechanism; these authors actually observed complement activation in seven out of eight anaphylactic reactions. High titres of IgG3 antibodies to L-asparaginase have been postulated by some investigators to be associated to a higher risk of anaphylaxis¹⁰⁹. Attempts have been made to predict L-asparaginase reactivity prior to its administration; the intradermal tests have produced both false-positive and false-negative results¹¹⁰, and the exposure test to small doses of the drugs has also had no predictive value¹⁰⁵. Recently, Bonno *et al.*¹¹¹ have reported the case of a girl with positive intradermal tests to L-asparaginase, in whom intravenous desensitisation could be successfully performed.

Substitutes for L-asparaginase have been searched for. For instance, L-asparaginase has been obtained from *Erwinia chrysantemii*, a plant pathogen. This L-asparaginase has a similar antitumoural efficacy spectrum but different antigenicity¹¹², and has been successfully used in patients who had had previous reactions to *E. coli*

L-asparaginase^{103,105,113,114}, although cases have been reported of reaction to the first dose of Erwinia L-asparaginase because of cross reactivity¹⁰⁵, or because of allergic reaction to this enzyme after having had an allergic reaction to *E. coli*-derived L-asparaginase¹¹⁵. Other molecular modifications have also been carried out on L-asparaginase, such as binding to peptide polymers. One of such modifications has been binding to polyethyleneglycol, originating a new substance named pegaspargase, with less immunogenicity and longer clearance time. In a recent review of available data¹¹⁶ it was concluded that pegaspargase represents a safe and effective alternative in the therapy of patients having developed hypersensitivity reactions to L-asparaginase derived from *E. coli* or *Erwinia carotova*, although routine substitution of pegaspargase for L-asparaginase is not recommended. Quite recently, Stone *et al.*¹¹⁷ have reported two cases of polyethyleneglycol-bound asparaginase anaphylaxis, one of them with a positive intradermal test to granulocyte colony stimulating factor (G-CSF) and the other one with negative skin tests but with a delayed urticarial reaction after testing. G-CSF is derived, by recombinant DNA technology, from *E. coli*, suggesting a possible sensitization to bacterial components. Both patients had negative skin tests and full tolerance to the granulocyte-macrophage colony-stimulating factor, GM-CSF, which is derived not from *E. coli* but from *Saccharomyces cerevisiae*.

Finally, one case of toxic epidermal necrolysis with L-asparaginase has been reported¹¹⁸.

PACLITAXEL AND DOCETAXEL

Paclitaxel

Paclitaxel is a complex alkaloid derived from the bark of the yew tree (*Taxus brevifolia*); chemically, it is a diterpenoid taxane. Although it shares some similar chemical structures with other natural alkaloids, paclitaxel contains one single taxane ring. The drug is highly lipophilic and is not water-soluble, so that it is administered in a polyoxyethylated castor oil (Cremophor EL) and 50% ethanol solution^{119,120}. Paclitaxel is the first one in a new class of chemotherapeutic agents, the taxanes. Hepatic metabolism and biliary excretion represent the major pathway for elimination of the drug¹²¹. Besides its haematological toxicity, paclitaxel may also induce hypersensitivity reactions, arrhythmias and neuropathy.

Paclitaxel inhibits cell division by promoting microtubule assembly and stabilisation through inhibition of tubulin depolymerisation, leading to the formation of aggregates of microtubules within the cell. The cell is thus blocked in the G2 and M phases and cannot build the mitotic spindle. Paclitaxel has a radiosensitising effect: cells in the G2 and M phases of the cell cycle, if affected by taxoids, are highly sensitive to radiation.

The toxicity of this chemotherapeutic agent is mainly haematological and neurological, and manifests also as asthenia and arthro-myalgia.

Paclitaxel is mainly used in the therapy of ovarian and breast carcinoma; lung cancer constitutes a further indication.

Hypersensitivity. The most frequently observed toxicity has been WHO grade I hypersensitivity¹²². The incidence is highly variable among the various series, and has even been reported to be 0% in some studies¹²³; it generally does not exceed 20%¹²⁴⁻¹²⁶.

Paclitaxel is administered under prophylactic measures for preventing hypersensitivity reactions, both in the first and in successive therapy courses. Premedication comprises corticosteroids (dexamethasone), and H₁ (diphenhydramine) and H₂ antihistamines (cimetidine)^{127,128}; this premedication is usually given intravenously 30 minutes before commencing the administration of paclitaxel¹²⁹, although in some cases oral corticosteroids administered 6 to 12 hours previously can also be used¹³⁰. Severe hypersensitivity reactions are rare with the use of these three antiallergic drugs, although mild reactions such as exanthemas are more frequent.

The patients develop reactions comprising skin rubefaction, hypotension, dyspnoea with or without bronchospasm, angioedema, sudoration, hyperhidrosis, urticaria or abdominal and limb pain; these reactions may be associated to bradycardia, a side effect of the drug itself. One half of these reactions occur within the first two or three minutes after the first dose of drug therapy. These clinical features correspond to those of type I hypersensitivity reactions¹²⁷. Severe life-threatening reactions occur in approximately 2% of the cases. They are more frequent with short infusion times and rarer if the infusion times are lengthened to 3-24 hours³; prolonging the infusion to 3 hours is usually enough to reduce the hypersensitivity reactions¹³¹.

The drug may be reintroduced in patients who have had hypersensitivity reactions; this can be done by prolonging the infusion time from 3 to 24 hours, particularly in

patients who have received premedication and whose reaction has not been severe^{132,133}. Controversy exists regarding the severe reactions; some authors propose reintroduction under premedication and with low infusion rates¹³⁴, while others consider that the drug can only be reintroduced when no other alternative is available¹³⁵.

In recent times, one-hour infusion schedules in weekly or tri-weekly courses have been used under premedication with the three drugs already mentioned, with similar activity in breast and lung cancer and with good tolerance and no increase in hypersensitivity reactions^{136,137}.

The formulation of paclitaxel includes a considerable amount of Cremophor EL; this compound may also be responsible for hypersensitivity reactions¹²⁰. Histamine release by Cremophor EL has been observed in some studies¹³⁸, but the release level was so low that it is considered improbable that this may be responsible for hypersensitivity reactions. Nevertheless, some authors state that paclitaxel is contraindicated in patients with a previous history of hypersensitivity reactions involving drugs that use Cremophor EL as solvent, such as cyclosporin and teniposide¹³⁹. In the dog, Cremophor EL has been observed to induce histamine release within 10 minutes after administration¹⁴⁰. *In vitro* studies on human blood have not confirmed this possibility¹⁴¹. Studies with the aim to better define whether paclitaxel itself or its excipient is the causative agent in hypersensitivity reactions have not been carried out. Other drugs formulated in polyoxyethylated castor oil have also been associated with similar reactions.

Parenteral desensitisation with paclitaxel has been carried out using ten-fold serial dilutions, and the patient was able to tolerate the therapeutic infusion without complications or need for corticosteroids or antihistamines¹⁴². In that same study, a histamine release test was performed with paclitaxel alone, with vehicle alone and with both, with positive results only for paclitaxel and not for the vehicle.

The mechanism of these hypersensitivity reactions is unknown, and it might well be a multifactorial one. It is unlikely that the reactions may be due exclusively to IgE antibodies to paclitaxel or to its Cremophor EL vehicle, as 56% of the reactions occur already with the first administration¹³¹. Severe anaphylactic reactions have been reported in the first course of paclitaxel therapy¹⁴³; such reactions may have been mediated by the release of histamine and other vasoactive substances from the mast cells and basophils¹²⁷.

Transient pulmonary infiltrates have been reported that may conceivably have been caused by hypersensitivity reactions to paclitaxel¹⁴⁴.

Docetaxel

Docetaxel is prepared from the leaves of the European yew (*Taxus brevifolia*). Clinical trials have shown it to be active in non-microcytic ovary, breast and lung cancer. Studies have also been carried out with favourable results in melanoma, renal-cell carcinoma, lung cancer, and head and neck and ovarian malignancies. The most important adverse side effect is haematologic toxicity; this drug may also cause fluid retention, ungual changes, erythematous skin reactions, nausea and vomiting.

Docetaxel is slightly more soluble and more potent than paclitaxel.

Hypersensitivity. In one study, hypersensitivity reactions were observed in 42% of the patients; these reactions were generally mild or moderate¹⁴⁵. Their characteristic features were pruritus, rubefaction, skin rashes, dyspnoea, hypotension and fever. Hypersensitivity reactions to docetaxel have in some cases been attributed to its formulation with polysorbate-80¹⁴⁶. Nevertheless, it is generally considered that the most probable mechanism is that of histamine release¹⁴⁷. The observed reactions may be blocked with the use of premedication^{148,149}.

Among the skin reactions reported there have been cases of onycholysis, finger- and toenail calcification, erythema, desquamation, pruritus and dry skin¹⁴⁵. The skin biopsies have revealed perivascular lymphocytic infiltrates as the expression of reaction to the drug. In some patients, this can be dose-limiting.

Cross reactivity between paclitaxel and docetaxel. No studies seem to exist assessing the cross reactivity between taxanes. Lokich and Anderson¹³³ describe four patients who had experienced hypersensitivity reactions with paclitaxel and who later tolerated docetaxel (given together with dexamethasone as an antiemetic). Although they did not carry out immunological studies, the authors suggest that the tolerance to docetaxel might be due to the fact that, unlike paclitaxel, it is not formulated with Cremophor EL.

TENIPOSIDE AND ETOPOSIDE

Teniposide (VM-26) and etoposide (VP-16) are semisynthetic derivatives of the epipodophyllotoxins, themselves derived from *Podophyllum peltatum*. They interact with the enzyme topoisomerase II, inducing links and breaks in the DNA strands. Although they only differ in a

methyl group in phenylidine in the glucopyranoside, teniposide appears to cause a greater number of hypersensitivity reactions³. The formulations of VM-26 and VP-16 both contain Cremophor EL.

Etoposide

This agent is used in the therapy of testicular cancer, of extragonadal germ cell tumours, lung cancer, leukaemias, lymphomas, Kaposi's sarcoma and other neoplasms. It can induce haematologic toxicity, nausea and vomiting.

Hypersensitivity. Anaphylactoid reactions occur in 1-2% of the patients, with chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension. These reactions respond to the discontinuation of the drug infusion and to therapy with vasopressors, corticosteroids, antihistamines and volume expanders. The onset of the reaction may occur after a few minutes of infusion or several hours after its end¹⁵⁰, but more frequently during the infusion of the drug. There are no known risk factors, and few patients have a past history of allergy¹⁵¹. Therapy with the agent may be continued if premedication is used and the infusion rate is slowed^{150,152}. However, cases have been reported in which the drug could not be reintroduced despite adequate premedication¹⁵³.

These reactions are more frequent in patients with leukaemia or lymphoma treated with polychemotherapy, with an incidence up to 51% among patients with Hodgkin's disease¹⁵⁴, although in that series the drug could be reintroduced in 78% of the cases. The same authors suggest that the changes in cell-mediated immunity in Hodgkin's disease may predispose these patients to drug hypersensitivity reactions¹⁵⁴.

Intravenous administration is believed to represent a risk factor for hypersensitivity reactions¹⁴⁷. No cases have been reported of such reactions with oral etoposide³.

The mechanism of hypersensitivity reactions to epipodophyllotoxins has not been sufficiently clarified. The fact that many reactions occur during the first exposure to the drug suggests a non-immunologic mechanism¹⁵².

One case of Stevens-Johnson syndrome in an adult patient undergoing his second course of VP-16 therapy for microcytic lung cancer has been reported. The time of presentation and the clinical circumstances suggest the possibility of a type III reaction through antibody response with immune complex deposition in the cutaneous vessels¹⁵⁵.

Teniposide

The efficacy spectrum of teniposide is very similar to that of etoposide, but it is more often used in children with acute lymphatic leukaemia. The frequency of reactions is greater than with etoposide. Myelosuppression, nausea and vomiting represent the main toxicities; this drug may also cause peripheral neuropathy and hypotension when infused rapidly.

Hypersensitivity. Anaphylaxis is rare with this agent, but other hypersensitivity reactions occur in 2-11% of the patients depending on the type of clinical trial¹⁵⁶. Their characteristic features are chills, rubefaction, urticaria, angioedema, hypotension, bronchospasm, tachycardia, fever or orbital oedema¹⁵⁷. Many of these reactions may occur upon the first administration of the drug¹⁵⁶⁻¹⁶⁰, suggesting that a non-immunologic mechanism may be involved. Experimental studies in dogs and mice have demonstrated an association between the administration of teniposide and release of histamine and other vasoactive substances¹⁶¹. It has also been demonstrated that teniposide may induce histamine release from basophils in blood samples from healthy, not previously exposed children, through a mechanism that is not IgE-mediated not related to the Cremophor EL vehicle¹⁴¹. The drug can usually be reintroduced under premedication¹⁵⁷, although this is not always possible¹⁵⁹.

Hypersensitivity reactions with teniposide appear to be more frequent in patients with brain tumours and neuroblastomas^{156,159}.

Cross reactivity. There is disagreement as to the existence of cross reactivity between etoposide and teniposide. Etoposide differs structurally from teniposide only in the substitution of a methyl group for a tenylidine one in the glucopyranoside moiety. However, teniposide more often causes hypersensitivity reactions. True cross reactivity does not seem to exist between these two agents^{139,147}.

ANTHRACYCLINES

A number of chemotherapeutic agents exist that belong to the anthracycline group. Daunorubicin is an antitumoural antibiotic derived from *Streptomyces coerulescens*, while doxorubicin -or adriamycin-, another anthracycline, is derived from *Streptomyces peucetius* var. *Caesius* and differs from daunorubicin only in a hydroxyl

group in the C-14 carbon atom. Epirubicin is a stereoisomer of doxorubicin. Mitoxanthrone is another anthracycline derivate, with less cardiologic toxicity.

The main toxicity of these agents is haematological; they may also induce cardiotoxicity, particularly in the case of doxorubicin. They also induce nausea, vomiting and alopecia.

Doxorubicin may be directly cytotoxic without penetrating into the neoplastic cells; it also intercalates into DNA and inhibits type I and type II topoisomerases. It may covalently bind to DNA and thus damage it, and it interferes with DNA uncoiling, reducing its synthesis. All these effects induce cell apoptosis.

The anthracyclines have a broad spectrum of activity, but they are used mainly in the therapy of acute leukaemias.

Hypersensitivity. Most of the anthracyclines have caused hypersensitivity reactions. Both daunorubicin and doxorubicin have induced such reactions when administered intravenously¹⁶²⁻¹⁶⁶ and even intravesically^{167,168}. Skin rashes occur in up to 3% of the patients receiving doxorubicin¹⁶⁹. Pretreatment with antihistamines and corticosteroids may reduce the severity of the reactions¹⁶⁶; however, these measures are not always effective: in one reported case the reaction recurred, in association to urticaria and bronchospasm, despite antihistamine pretreatment¹⁶⁵. No hypersensitivity reactions have been reported with the oral administration of anthracyclines³. There are also reports of one case of angioneurotic oedema secondary to the administration of doxorubicin¹⁷⁰, and of pruritus, oedema and urticaria in the site of injection^{169,171} attributed to extravasation or to histamine release¹⁶⁵. The mechanism of the hypersensitivity reactions to the various anthracyclines is unknown. Crowther *et al.*¹⁷² have reported one case of urticarial reaction after the administration of daunorubicin that reappeared upon the administration of adriamycin (doxorubicin).

Hypersensitivity reactions have also been reported with mitoxanthrone, a synthetic amino-anthrachinone, although with very low frequency¹⁷³.

Allergic contact dermatitis has also been described in association to epirubicin, another anthracycline¹⁷⁴. The patient developed the reaction with the first dose of the drug; however, the patch test with epirubicin was positive. Considering that the patient had previously tolerated mitomycin, the authors suggest the possibility of cross reactivity between this drug and epirubicin.

Cross reactivity. There is only one reported case of cross reactivity, between daunorubicin and doxorubicin¹⁷². This patient developed a severe urticarial reaction after the administration of daunorubicin, with recurrence after doxorubicin. The very great structural similarity between these two agents must however be stressed. In the case of mitoxanthrone, Taylor *et al.*¹⁷³ have reported one patient who tolerated doxorubicin after having had a reaction with tachypnoea, cyanosis and hypotension after the administration of mitoxanthrone.

Cross reactivity may occur between doxorubicin and lincomycin¹³⁹.

BLEOMYCIN

This is an antineoplastic antibiotic, isolated in 1962 from a variety of *Streptomyces verticillus*. It binds to DNA and induces breakage of its strands.

Bleomycin is indicated in epidermoid carcinomas, including those of the cervix, external genitalia, oesophagus, skin, head and neck; it is also used in Hodgkin's disease, in bladder, lung and thyroid cancers, and in the therapy of malignant effusions.

This chemotherapeutic agent may induce lung fibrosis, skin erythema and hyperpigmentation and frequently fever, which may be associated to cardiovascular collapse and even death¹⁷⁵.

Hypersensitivity. There are very few cases reported of reactions suggesting hypersensitivity. In one of these, a patient was described who developed angioedema, erythematous-haemorrhagic exanthema and eosinophilia, with fatal outcome, although the reaction occurred two days after the administration of the first bleomycin therapy course¹⁷⁶. A subcutaneous test had been previously performed with 2 ml bleomycin sulfate without eliciting any reaction. One case of toxic epidermal necrolysis has also been reported, in one patient who had received therapy with unusually high doses of bleomycin¹⁷⁷. One further case of fatal outcome after the administration of a low dose has also been reported¹⁷⁵. One characteristic finding with bleomycin is that of "whiplash" dermatitis.

There is a form of bleomycin-induced pulmonary toxicity, which is dose-dependent and seldom occurs with less than 300 Units^{67,178}. The condition is a pneumonitis in which polymorphonuclear accumulation is first observed, followed by a T-lymphocyte infiltrate; there is increased chemotactic activity of the alveolar macrophages. The his-

tologic examination discloses pneumocyte hyperplasia with eosinophil-rich infiltrates¹⁷⁹. The pathophysiologic mechanisms of these lesions are hotly debated; some authors invoke a direct toxic action of bleomycin, while others advocate a hypersensitivity mechanism⁶⁷.

MITOMYCIN C

This antitumoural antibiotic was isolated in 1958 from *Streptomyces caespitosus*. It binds to the guanine or cytosine bases in DNA, forming bonds and bridging and inhibiting its function and synthesis.

Mitomycin C is used intravesically in bladder cancer. It is used in combination with other chemotherapeutic agents, and evidences modest activity against a wide range of neoplasms. Its fundamental toxicity is delayed myelodepression; it may also induce a haemolytic-uraemic syndrome and lung toxicity.

Hypersensitivity. Mitomycin C is usually given intravenously. Cases have been reported of generalised vesicular rashes suggesting an allergic reaction, although the underlying mechanism has not been investigated^{3,180}. The risk of skin rash with mitomycin C may increase when the drug is combined with vincristine and bleomycin or doxorubicin¹⁸⁰. One case has also been reported of a local erythema multiformis-like eruption after the administration of mitomycin and 5-fluorouracyl, with erythematous papules in the proximal area of the forearm into which the drugs had been infused which histologically suggested a reaction similar to that of erythema multiformis, so that a localised hypersensitivity reaction to mitomycin C was suspected¹⁸¹. Although infrequently, cases have been reported of skin exanthemas after intravenous administration of mitomycin C¹⁸⁰. One case has been reported of acute respiratory failure with fatal outcome after the administration of mitomycin and vinblastine, in a patient with metastatic breast cancer, and an acute hypersensitivity reaction was suggested as the cause of the adult respiratory distress syndrome¹⁸². There is also a form of pneumopathy after administration of mitomycin, occurring within the first six months of therapy, which presents a histological picture of fibrosis but has a benign evolution after discontinuation of the drug even though severe, rapidly fatal forms are known⁶⁷.

Mitomycin is administered intravesically as topical medication in the therapy of epithelial tumours of the urinary bladder. Hypersensitivity reactions are much more frequent with this route of administration. Local toxicity

consists of chemical cystitis, occurring in over 10% of the patients. After cystitis, skin reactions represent the most frequent side effect, consisting of disseminated dermatitis, or a vesicular form involving the hands and/or feet and the genital or perianal region, or urticaria, sometimes with associated fever or general malaise¹⁸³. Over 9% of the patients treated with mitomycin C develop cutaneous side effects; almost 3% of them must eventually discontinue therapy because of the severity of the dermatologic reactions¹⁸⁴. Most of the reactions are believed to be due to the absorption of mitomycin C through the vesical mucosa (ca. 1% of the instilled dose) and not to direct contact, although the latter may also occur. Diffuse or generalised reactions are more probably due to a systemic contact dermatitis caused by a delayed hypersensitivity reaction. The following observations appear to support this hypothesis: the skin reactions develop after several instillations; after a first skin reaction, the reintroduction of the drug reproduces the symptoms; finally, it is possible to demonstrate the presence of CD1+ antigen-presenting cells in the bladder wall and of positive patch tests with mitomycin C in the patients with skin lesions¹⁸⁵.

METHOTREXATE

Methotrexate is a folate analogue, and has L-leucovorin as its antidote. The drug induces a reduction in the synthesis of the nucleotides purine and pyrimidine, through competition at the dihydrofolate reductase level. It is a phase-specific antineoplastic drug.

This agent is used in the therapy of leukaemias and lymphomas, in cancer of the head and neck, breast cancer, gestational neoplasms of trophoblastic origin, mycosis fungoides, and osteosarcoma. Its main toxicities are haematologic, hepatic and renal; it may also induce chills and fever.

Three different administration schedules are used: a standard oral or parenteral dose, intrathecal administration, or high-dose therapy followed by leucovorin rescue. The intrathecal route is used in meningeal carcinomatosis, while the high-dose schedule with leucovorin rescue is applied in the adjuvant therapy of osteosarcoma and in acute leukaemias.

Hypersensitivity. Hypersensitivity reactions to methotrexate are infrequent and include anaphylaxis, urticaria, angioedema, acute pneumonitis, cutaneous vasculitis, severe epidermic toxicity, haemolytic anaemia and hepatic

tis. A number of anaphylactic reactions have been published in the literature, usually after previous exposure to either high or low doses of the drug¹⁸⁶⁻¹⁹¹. Alkin *et al.*¹⁹² describe two cases of immediate hypersensitivity reactions during the first administration of methotrexate; the patients were two young males with osteosarcomas in different locations, with no known history of hypersensitivity. One of them developed generalised pruritus, urticaria, angioedema and laryngeal oedema, and the other one pruritus and generalised urticaria. The reactions occurred 13 and 30 minutes after the infusion, respectively, and remitted under conventional therapy. Lacking previous exposure to methotrexate, these reactions are described as anaphylactoid and represent a possible ability of the drug for inducing direct mast cell degranulation or complement activation¹⁹². In one of the two cases the drug was subsequently reintroduced under premedication. There is one other report of an anaphylactoid reaction that could also be prevented with premedication¹⁸⁶. Cohn *et al.*¹⁹¹ describe one case of anaphylaxis after low-dose methotrexate with onset after six therapy courses; the patient developed disseminated erythema after an intradermal test with methotrexate. In Spain, Vega *et al.*¹⁸⁹ have reported a case of methotrexate anaphylaxis. The patient, a female, had a positive prick test although it was not possible to detect specific IgE and the histamine release test was negative.

Oral methotrexate may cause agranulocytosis in patients with rheumatoid arthritis. Although a toxic effect cannot be excluded, some authors^{193,194} have suggested a type II hypersensitivity mechanism. A type II haemolytic reaction has also been reported in which IgG3 antibodies reacted with the erythrocytes in the presence of methotrexate causing haemolysis. The antibody did not bind complement but sensitised the erythrocytes, which were then phagocytosed by macrophages³.

Acute pneumonitis may be induced via a type III hypersensitivity mechanism⁶⁷. This condition is characterised by peripheral blood and/or pulmonary eosinophilia, bilateral hilar lymphadenopathies, exanthema, rapid onset with no relation to the dose or duration of therapy, and resolution after withdrawal of the drug and corticosteroid administration. This phenomenon may be induced by any dose of the drug, even those used in the management of other conditions such as rheumatic diseases⁶⁷. Hypersensitivity pneumonitis represents a potentially fatal side effect in patients with rheumatoid arthritis treated with methotrexate¹⁹⁵. Two different groups of investigators have demonstrated increased numbers of lymphocytes in the bronchoalveolar

lavage fluid of patients with this form of methotrexate reaction, suggesting an immunologic mechanism¹⁹⁶.

Another form of hypersensitivity reaction is vasculitis¹⁹⁷. Purpuric cutaneous lesions develop that disappear upon discontinuation of methotrexate and reappear upon reintroduction of the drug. One case of necrotising vasculitis has also been reported, after two injections of low-dose methotrexate in the management of rheumatoid arthritis¹⁹⁸.

There is one description of fulminant hepatic failure after the administration of intermediate-dose methotrexate, in a patient with non-Hodgkin lymphoma¹⁹⁹. The lymphocyte transformation test was strongly positive. The necropsy findings showed that there was no inflammatory infiltrate in the liver but demonstrated marked biliary congestion, which is the hallmark of drug-induced hepatitis. Because of these findings, it seems plausible that this case of fulminant liver failure may have been a case of allergic reaction to methotrexate.

Trimetrexate, an analogue of methotrexate, may induce cutaneous eruptions with generalised erythrodermia, which usually occur some days after the administration of the drug and resolve within one week. The mechanism of this cutaneous toxicity is unknown²⁰⁰. Grem *et al.*²⁰¹ have described five cases of hypersensitivity reactions after the administration of trimetrexate.

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