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Feature Articles

What is the Place of Carboplatin in Paediatric Oncology?

François Doz and Ross Pinkerton

INTRODUCTION

THE FIRST experimental evidence of the cytotoxic effect of cisplatin was reported in 1965 [1]. The use of this drug in paediatric oncology practice dates from the end of 1970s [2]. Its use is limited by cumulative toxicity (hearing and renal impairment) [3]. However, the high activity of this drug in numerous childhood tumours has made this drug an essential component of paediatric oncology practice. In an attempt to improve the therapeutic index, a number of platinum analogues have been synthesised. The main analogue used at present is cis-diaminodicarboxylato-cyclobutane-platin (carboplatin), whose indications in solid tumours of childhood are becoming more and more numerous. In this review we consider the pharmacodynamic characteristics and the pharmacokinetics of carboplatin compared to cisplatin, its current indications, toxicity and possible future use in children.

PHARMACODYNAMICS

Mechanism of action

The essential mechanism of action of platinum derivatives is the covalent binding by the diamino platinum radical with DNA: this has been mainly studied with cisplatin [1]. As with cisplatin, the amine radicals of carboplatin are not modified while mono or dicarboxylatocyclobutane radicals bound to the platinum atom are hydrolysed. The hydroxyl groups substituted in this way are capable of reacting with the molecular targets on intranuclear DNA [4]. This can be either between the same strand of DNA (intrastrand link) or between two complementary strands (interstrand link). The second mechanism of interaction, although quantitatively less important, seems to be the determinant of the drugs cytotoxicity. A modification in the structure of DNA induced by this linkage impairs cell replication. The essential difference between cisplatin and carboplatin is the kinetics of this linkage to DNA. The hydrolysis of cisplatin is much more rapid, and the speed of linkage with DNA is also greater [5]. The linkages between the diaminoplatin radical with intracytoplasmic RNA or with proteins of the membrane cytosol or the nucleus are probably equivalent, but their role in the drug's cytotoxicity is uncertain.

Mechanisms of resistance

These are better known for cisplatin than for carboplatin and comprise at least four mechanisms [6, 7]:

1. A reduction in the entrance of drug into the cell (or an increase in its efflux) [8].
2. Repair mechanisms which restore the intact DNA molecule after excision of the segments of DNA to which the diaminoplatin radicals are bound [9]. This mechanism is one of the theories for the synergy described *in vitro* between platinum compounds and the epipodophyllotoxins. The latter inhibit topoisomerase II, an enzyme implicated in the repair of DNA.
3. Intracytoplasmic chelation of platinum by thiol groups: glutathione in the form of GSH (reduced glutathione) [10] or metallothionein [11]. The consequence of this is a reduction in the proportion of drug which reaches its principal target, intranuclear DNA. The modulation of the intracytoplasmic pool of the thiol radical has been proposed as a method of improving the therapeutic index of platinum derivatives by inhibiting the synthesis of GSH, specifically in tumour cells, or by increasing the cellular concentration of metallothionein in normal tissues.
4. Finally, the amplification of certain oncogenes within the *ras*, *fos* and *myc* families has been associated with increased resistance to cisplatin *in vitro* [12, 13]. To date, it is not known precisely which biological mechanisms related to oncogene amplification affect platinum derivatives' cytotoxicity.

PHARMACOKINETICS

Pharmacokinetic parameters

One of the most characteristic features of platinum derivatives is their covalent binding to plasma protein. The diaminoplatin radical binds particularly at the level of thiol groups. Protein binding is not a mechanism of drug transport but represents a mechanism of inactivation as, once bound covalently to protein, the diaminoplatin radical is unable to interact with the molecular target on DNA.

Thus, the only form of circulating drug which is potentially active is the free form, unbound to either plasma protein or erythrocytes. This fraction is capable of undergoing intracellular hydrolysis and reacting with DNA. Pharmacokinetic studies of platinum derivatives are usually performed using flameless atomic absorption spectrometry [14–16], which does not enable separation of different drug metabolites. The free drug can be estimated by ultrafilterable platinum, which is probably the most relevant pharmacokinetic parameter, and should be distinguished from total plasma platinum.

The difference in pharmacokinetic behaviour of cisplatin and carboplatin is explained essentially by the greater rate of hydrolysis of cisplatin. Thus, by comparison to cisplatin, carboplatin is less rapidly bound to plasma proteins, has a higher proportion of free ultrafilterable drug, a longer half-life of free and of bound drug and, finally, a faster elimination in urine [15, 17, 18].

Dose formula for carboplatin

Although the pharmacokinetic behaviour of many active cytotoxic drugs has been documented, this is often multifactorial and subject to many variables. Carboplatin is an exception in that it is almost entirely excreted by the kidneys through glomerular filtration. For this reason, the elimination half-life is closely correlated with the glomerular filtration rate (GFR), and the area under the concentration curve (AUC) can, therefore, be predicted from a variety of methods of assessing renal clearance. This provides the potential for patient-specific dose regimens calculated from studies of renal clearance. In this way a target AUC can be achieved which will correlate with toxicity and possibly with cytotoxic activity. Studies in adults have shown that such a formula can be used to predict AUC [19, 20] and attempts are currently underway to derive a comparable formula for paediatric patients. Initial studies applying the adult formula to children were inaccurate because of overestimation of non-renal clearance, which is mainly due to reactions with tissue and plasma proteins, and has been shown to correlate with total body mass. Recently, Newell and colleagues have derived a formula based either on total body weight or total body water, which may provide a more accurate prediction for the small child [21].

The precise target AUC in paediatric practice is a controversial issue [22]. In adults with malignant teratoma poor outcome was shown in patients with an AUC less than 4 (mg/ml.min). In the current United Kingdom Children's Cancer Study Group (UKCCSG), a target AUC of 6 is used for germ cell tumour therapy. This is equivalent in a patient with normal renal function to a dose of around 500–600 mg/m^2. In regimens using higher dose carboplatin, such as for osteogenic sarcoma or neuroblastoma, a target AUC of around 8–10 would probably be necessary to produce comparable activity to the dose of cisplatin generally used. When carboplatin is incorporated into megatherapy regimens using bone marrow rescue, an AUC of 20 is comparable to 2–2.5 g/m^2. This dose has been shown to be tolerable in pilot studies using a GFR-based formula for dosage. It is particularly important when very high dose carboplatin is being given as a single high dose to be able to predict accurately the AUC. There is little point giving a child with very high renal clearance a dose based on surface area, if the eventual AUC ends up at less than 10. Conversely, in a child with impaired renal function, a dose of 2 g/m^2 may be anticipated to cause severe toxicity.

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It has recently been shown in adults that AUC can be correctly estimated with limited plasma sampling [23]. If this is confirmed in children, another way to realise dose adaptation, when carboplatin is given as a fractionated daily infusion, might be to adapt the dosage of carboplatin according to the measured AUC after the first infusion.

Tissue distribution

Because of the pharmacokinetic characteristics, the volume of distribution of carboplatin is proportionally less than that of cisplatin. However, animal studies have shown that the diffusion of carboplatin may be particularly impressive in certain tissues. Thus, the superior penetration into brain tissue by carboplatin [24], probably as a result of the greater gradient of free drug across the blood–brain barrier, makes this drug an attractive candidate for treatment of brain tumours in comparison to cisplatin [25]. Moreover, the good diffusion of carboplatin into haemopoietic tissues [24], as indicated by its striking haematological toxicity, has led to suggestions that carboplatin may have advantages over cisplatin in the treatment of haematological malignancies.

The problem of cross-resistance

The existence of cross-resistance between cisplatin and carboplatin depends to some extent on the pharmacodynamic characteristics and the pharmacokinetics of the two drugs. It has been well established at the experimental level where the interaction of platinum derivatives with DNA [5] or their cytotoxicity in tumour cell lines [25] was studied. This cross-resistance is not surprising as the principal mechanisms of action, and most of the mechanisms of resistance (increased DNA repair and thiol chelation) are thought to be the same for both cisplatin and carboplatin. The concept of dose equivalents between cisplatin and carboplatin is not easily transferred from laboratory to clinic. Carboplatin concentrations at least 10 times higher than cisplatin are necessary to produce the same cytotoxic effects *in vitro* [5]. In clinical practice, the haematological toxicity of carboplatin is a dose-limiting factor and, in conventional dose chemotherapy, only four to six times the cisplatin dose is generally used. However, in the case of *in vivo* treatment of certain tumours, other factors, such as different tisue penetration or local conditions regarding drug hydrolysis, particularly at the level of tumour cells, may perhaps lead to an advantage for carboplatin, despite cross-resistance observed *in vitro*.

TOXICITIES

Haematological toxicity

This is a dose-dependent toxicity and the limiting toxicity of carboplatin. It is particularly marked for the platelet lineage. Phase I studies of carboplatin in children have demonstrated this to be less severe than in adults, thus allowing the use of higher doses in this age group [26]. Because of improved supportive care (broad spectrum antibiotics during febrile neutropenic episodes, blood product transfusion availability), haematological toxicity, which is short term, can be fairly easily managed, and thus the short- and long-term consequences for haemopoiesis are less important than those of renal or auditory toxicity. The haematological toxicity is cumulative and the use of high doses of carboplatin, generally associated with other marrow suppressive drugs, will increase the risk of myelosuppression during successive treatments. Finally, pre-existing renal insufficiency markedly increases the risk of haematological toxicity associated with carboplatin [20].

The dose effect is one of the main principles of cancer chemotherapy, whereby increasing the drug dose also increases its antitumour effect [27]. While dose escalation of cisplatin is limited by renal and auditory toxicity, the haematological toxicity of very high dose carboplatin may be limited by the use of autologous stem cell transfusion and/or utilisation of bone marrow growth factors [28, 29]. Unexpectedly high incidences of veno-occlusive disease and fungal deaths have been associated with high-dose carboplatin regimens given to patients who have previously received cisplatin [30]. Although the use of the most readily available haematopoietic growth factors granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage CSF (GM-CSF) does not produce any reduction in the degree of thrombocytopenia, recent data show a reduction of carboplatin-induced thrombocytopenia with the use of interleukin-1α [31].

Nephrotoxicity

Although not negligible [32], the risk of renal toxicity with carboplatin is much less than with cisplatin. However, under two circumstances, it is necessary to monitor closely renal function prior to using this drug [15]: firstly, when using very high dose carboplatin, such as in high dose combination chemotherapy with autologous bone marrow rescue; and, secondly, when there is known renal dysfunction. In both situations, delay in the elimination of carboplatin will not only predispose to severe haematological toxicity but also possibly to nephrotoxicity.

Whether renal function should be monitored routinely following carboplatin use in children is controversial [33]. Association with other nephrotoxic treatments, either anti-tumour treatments (chemotherapy such as ifosfamide or abdominal irradiation) or supportive care treatments (aminoglycosides, antifungals such as amphotericin B or high dose acyclovir) may predispose to the risk of renal damage. Even if the immediate effects of carboplatin on renal function are less than that of cisplatin [34], one cannot necessarily conclude that there is a complete absence of long-term effects.

Neurotoxicity

In children the neurotoxicity of cisplatin is predominantly limited to sensory dysfunction, namely ototoxicity [35]. This is due to the accumulation of cisplatin in the organ of Corti, and leads to deafness which initially involves the high frequencies. This necessitates regular surveillance hearing tests: free field audiometry or evoked auditory potential in the very young child or formal audiography in older children. This ototoxicity is also cumulative. Carboplatin is reputedly non-ototoxic, but the use of very high cumulative doses, particularly when there is prior renal insufficiency which delays elimination of the drug, will lead to a potential risk of hearing dysfunction [36].

Long-term surveillance of hearing in infants pretreated with carboplatin must, therefore, be careful, particularly when other potentially ototoxic treatments have been given (some antibiotics, furosemide and irradiation of the central nervous system) [37]. This surveillance should be continued even if examination at the end of treatment is normal to exclude late deterioration.

Intestinal toxicities

Carboplatin is less emetogenic than cisplatin, although strong anti-emetic treatment is still often required. The use of the new classes of anti-emetics, the $5HT_3$ (serotonin) antagonists [38] is justified following the use of carboplatin, particularly when used at high doses. Mucosal toxicity and diarrhoea have also been

described following the use of high-dose carboplatin with autologous bone marrow rescue.

Mutagenic effects

The binding between the diaminoplatin radical and DNA encourages mutation [39] in a manner analogous to the mutageneis associated with alkylating agents. This mutagenic ability could lead to the risk of secondary tumours or leukaemia [40]. Such toxicity has recently been described in 2 patients previously treated for osteogenic sarcoma using cisplatin, methotrexate and doxorubicin but without an alkylating agent. Both developed secondary myeloid leukaemia 3 and 4 years after initial therapy [41]. Only long-term follow-up of patients treated with carboplatin will clarify the incidence of such long-term complications.

Reproduction

The limited risk of hypofertility in males after cisplatin treatment for testicular cancer is well known but has to be analysed according to other associated treatments [42]. Experimental studies have shown some risk of male hypofertility after carboplatin treatment [43]. There is, therefore, a possible risk of sterility in patients previously treated with carboplatin during childhood, particularly in males, but no data are yet available.

METHODS OF ADMINISTRATION

One of the advantages of carboplatin in paediatric practice is the easy mode of administration with the use of short-term infusion. For standard doses of carboplatin, hospital admission is not required. Compared to cisplatin, it seems less justified to use carboplatin as a continuous infusion, taking into account its spectrum of toxicity (relatively limited renal and auditory) and its pharmacokinetic characteristics (prolonged half-life of the free drug). In any case, for the treatment of brain tumours, short-term infusion is probably preferable in order to increase the passage across the blood–brain barrier [15].

Some experimental evidence suggests that myelotoxicity is reduced when the drug is given at night compared to during the day [44]. This effect has not, however, been demonstrated clinically.

CLINICAL INDICATIONS

Currently, the role of carboplatin in children can only be evaluated with certainty either from single-agent studies [45], or by analogy with phase II or phase III study results in adults, such as in the case of malignant germ cell tumours. In children, single agent studies are relatively uncommon and phase II studies often involve the empirical combination of carboplatin with other drugs. Three principles define the clinical indications of carboplatin: firstly, because of the lower risk of long-term nephro- and ototoxicity, carboplatin should be used in preference to cisplatin if at all possible, particularly in patients with a good prognosis; secondly, proven efficacy of cisplatin in a particular disease does not necessarily mean that carboplatin can "replace" cisplatin and does not preclude the need for clinical studies to evaluate the efficacy of carboplatin; thirdly, clinical studies might show activity for carboplatin in diseases where cisplatin had not been proven to be of value.

Currently, the indications for cisplatin include neuroblastoma [46], brain tumours [47], in particular medulloblastoma and

Table 1. Main combinations including carboplatin in standard dose chemotherapy in children

Reference	Diagnosis	Drugs	Total dose/course (mg/m²)	Daily dose	Duration of infusion (h)
22	Mixed diagnosis	Carboplatin	Target AUC*	Adapted (day 1)*	1
		Ifosfamide	4000	2000 (days 2,3)	0,25
		VP-16	200	100 (days 2,3)	1
65	Medulloblastoma	Carboplatin	800	160 (days 1–5)	1
		VP16	500	100 (days 1–5)	1
67	Brain tumours	Carboplatin	1000	500 (days1–2)	2
	("JET")	VP-16	300	100 (days 1–3)	1
72	Neuroblastoma	Carboplatin	800	160 (days 1–5)	1
		VP16	500	100 (days 1–5)	1
74	Germ cell tumours	Carboplatin	Target AUC**	500–700 (day 1)	1
	("JEB")	VP-16	360	120 (days1–3)	1–3
		Bleomycin	15	15 (day 2)	24
77	Nephroblastoma	Carboplatin	800	160 (days 1–5)	1
		VP-16	500	100 (days 1–5)	1
80	MMT	Carboplatin	500	600 (day 1)	1
		Vincristine	3	1.5 (days 1,8)	Bolus
		Epirubicin	150	150 (day 1)	3
Unpublished	MMT	Carboplatin	600	600 (day 3)	24
data	("VINCAEPI")	Vincristine	1.5	1.5 (day 1)	24
	SIOP protocol	Tenoposide	150	150 (day 4)	4
Unpublished	Neuroblastoma	Carboplatin	500	500 (day 1)	1
data	("OJEC")	Vincristine	1.5	1.5 (day 1)	Bolus
		Cyclophosphamide	600	600 (day 1)	Bolus
		VP-16	200	200 (day 1)	4

*The dose of carboplatin is adapted to Tc 99m-DTPA renal clerance (GFR) (ml/min/m²) according to the formula: dose (mg/m²) = target AUC × {(0.93×GFR)+15} where AUC is the area under the curve of the ultrafilterable carboplatin. **The dose of carboplatin is adapted to Cr 51-EDTA renal clearance (GFR) (ml/min) according to the formula: dose (mg) = target AUC × {GFR+(15×SA)} where SA is the body area. Target AUC is 6 mg×min/ml. MMT, malignant mesenchymal tumours.

other primitive neuroectodermal tumours (PNET) [48], retinoblastoma [49], hepatoblastoma [50], malignant germ cell tumours [51], osteosarcomas [52] and undifferentiated nasopharyngeal carcinoma [53].

The main problem is to define to what extent carboplatin can or should replace cisplatin for these diseases, and if it could have a useful role in other tumour types. There are some examples where carboplatin seems superior [15]: high dose chemotherapy regimens using autologous bone marrow rescue, treatment of brain tumours [25, 54] or in the presence of pre-existing renal insufficiency. Carboplatin is now part of numerous high-dose chemotherapy protocols [28, 55–62]. The use of haematopoietic growth factors after high doses of carboplatin [29, 31, 63] might decrease its myelotoxicity and/or allow higher doses of the drug to be given. Carboplatin might also be used before collecting circulating haematopoietic stem cells by leukaphoresis; reinjected, these circulating stem cells can be used to reduce the toxicity of further treatments [29].

Impressive efficacy has been shown in phase II studies in medulloblastoma and other PNETs [64–67]. With malignant glial tumours, its efficacy seem less encouraging [68] but relatively low doses have been used. However, very interesting activity has been noted in brain stem glioma [69] and also in low grade supratentorial glioma [70, 71].

With regard to tumour types where cisplatin is known to be active, equal efficacy associated with carboplatin has already been demonstrated for certain of these, for example, neuroblastoma [72, 73] and malignant germ cell tumours [74]. However, recent studies in adults with malignant germ cell tumours have shown cisplatin to be better than carboplatin in good risk cases [75], although this may reflect lower doses of carboplatin being used. The role of carboplatin is currently under study in other tumour types such as retinoblastoma, hepatoblastoma [76], osteosarcoma and nasopharyngeal carcinoma.

There is also the potential value of carboplatin in tumours where cisplatin has not been traditionally used. Its activity has recently been reported in patients with refractory or relapsed nephroblastoma [77], for whom one would not wish to use cisplatin because of compromised renal function. The extent of carboplatin diffusion into haemopoietic tissue and preliminary clinical studies in adults [78, 79], encourage the study of this drug's activity in leukaemias and lymphomas of childhood. Finally, it would also be of interest to assess the activity in tumours where cisplatin is not generally found to be particularly effective, such as in Ewing's sarcoma or soft tissue sarcomas. Despite lack of clear single-agent activity, carboplatin is currently used incorporated in both relapse and metastatic regimens of the SIOP malignant mesenchymal tumours (MMT) group [80].

COMBINATION THERAPY

Carboplatin in combination chemotherapy (Tables 1 and 2)

Often carboplatin is associated with epipodophyllotoxins (VM26 or VP16) on the basis of the synergy well established *in vitro*. The clinical efficacy of this association is often reported in childhood cancer [65, 67, 72, 74, 77].

Additive or synergistic antitumour effect is a principle also utilised in other associations, particularly with the anthracyclines [80], and also with alkylating agents, particularly in several high-dose chemotherapy regimens using bone marow rescue [28,

Table 2. Main combinations including carboplatin for high dose chemotherapy in children

Reference	Diagnosis	Drugs	Total dose (mg/m²)	Daily dose	Duration of infusion (h)
28	Mixed diagnosis	Carboplatin	1500	500 (days 4–6)	1
		Melphalan	120–140	30–32.5 (days 1–4)	0.5
		VP-16	1800	1800 (day 5)	4
		TBI	12 Gy	3 Gy	
57	Neuroblastoma ("OMEC")	Carboplatin	Target AUC*	200–350 (days 1–5)	1
		Melphalan	180	180 (day 6)	5 min
		VP-16	1000	200 (days 1–5)	3
		Vincristine	4	1.5 (day 1)	Bolus
58	Neuroblastoma (modified OMEC)	Carboplatin	1000	2.5 (days 1–5)	24
		Melphalan	180	1000 (day 1)	1
		VP-16	250	180 (day 1)	Bolus
		Vincristine	1.5	250 (day 1)	4
59	Mixed diagnosis	Carboplatin	900–1980	1.5 (day 1)	Bolus
		Ifosfamide	10000–18000	300–660 (days 1–3)	24
		VP-16	600–1500	2500–4500 (days 1–4)	2
				200–500 (days 1–3)	1.5–2
60	Mixed diagnosis	Carboplatin	1200–2100	(two daily fractions)	
		VP-16	960–1500	400–525 (days 1,3,5)	1
				320–500 (days 2,4,6)	6
61	Neuroblastoma and soft tissue sarcoma	Carboplatin	1250–1800	250–360 (days1–5)	1
		Melphalan	180	180 (day 6)	5 min
62	Retinoblastoma	Carboplatin	1750	350 (days 1–5)	1
		VP-16	1750	350 (days 1–5)	1
		Cyclosphosphamide	6400	1600 (days 2–5)	1

*The dose of carboplatin is adapted to Cr 51-EDTA renal clerance (GFR) (ml/min) according to the formula: dose (mg) = target AUC × {GFR+(15×SA)} where AUC is the area under the curve of the ultrafilterable carboplatin and SA the body area. Target AUC is 20 mg×min/ml. TBI = total body irradiation.

55–62]. This concept is of particular potential benefit where there is little overlapping toxicity between the agents combined and, for this reason, it has been proposed to combine carboplatin with cisplatin [81].

Non-chemotherapy combinations

Experimental work has attempted to reduce the toxicity to normal tissues [82, 83] or increase the activity in tumour tissue, in particular by reducing the cellular pool of glutathione in the form of GSH. Such strategies are already under evaluation in adults treated with cisplatin with some encouraging results [84] but these have not yet been evaluated in childhood or with carboplatin.

As for cisplatin, some experimental evidence suggests a radiosensitising effect of carboplatin [85]; little is known about a possible potentiating effect with hyperthermia [86].

Carboplatin and biological therapy

Encouraging preliminary results from a combination of cisplatin and interleukin-2 have recently been reported in adults [87] but not yet studied in children or using carboplatin.

CONCLUSIONS

Since the discovery of the cytotoxicity of cisplatin due to the platination of DNA and its utilisation as anticancer chemotherapy, there has not been another cytotoxic drug with such an original mechanism of action or similar antitumour activity. The discovery and development of the analogue carboplatin, whose limiting toxicity is haematological, allows the reduction of long-term nephro- and ototoxocities, and may perhaps increase the range of indications for platinum therapy. Individual dose adaptation of carboplatin should be possible according to its pharmacokinetics and application of a dose formula based on renal function. Finally, the combination of carboplatin with other agents, while currently widely used, is in some cases unfounded. Clearer data regarding single-agent activity in many conditions are urgently required.

The role of carboplatin in a limited number of children's cancers is today clearly established, and further research is needed to optimise the drug's use, with regard to dose, scheduling and synergistic combination.

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Does Improved Control of Tumour Growth Require an Anti-cancer Therapy Targeting Both Neoplastic and Intratumoral Endothelial Cells?

Giampietro Gasparini and Adrian L. Harris

INTRODUCTION

MOST HUMAN metastatic solid tumours are not currently curable with any kind of systemic anticancer therapy (i.e. chemotherapy, hormone therapy and immune therapy), and the mortality caused by the "four major killer tumours" (lung, colorectal, breast and prostate cancers), has not significantly decreased in recent years [1]. This is due to the fact that some solid epithelial tumours are not sensitive to chemotherapy [2, 3], and that those which are initially sensitive may develop acquired resistance after exposure to drugs (see [3] and references therein). Thus, there is now a critical need for new therapeutic strategies in the hope of improving tumour growth control in the future. It seems appropriate to speculate that the search for the genetic and biochemical changes that lead to malignancy is an important strategy to identify the key stages of tumour transformation and the process of metastasis [4]. Identification of specific biological targets could also provide new opportunities for developing rationally designed biological therapies for cancer [4–6]. These new targets include oncogenes, growth factors and their receptors, signal transduction pathways, cell differentiation signals [6, 7], antisense inhibitors of gene expression [8], gene deletion [9] and tumour angiogenesis [10].

One of the most promising of these is the discovery of specific angiogenesis inhibitors. As stated by Marx [4], "researchers are sufficiently hopeful about the anti-angiogenesis approach to cancer therapy that they are beginning clinical trials".

THE BIOLOGICAL BACKGROUND

Before the 1960s, it was believed that the only relevant phenomenon related to tumour vascularisation was the dilation of blood vessels from normal tissues surrounding the tumour (hyperaemia) [11].

Research begun about 25 years ago by Folkman and associates, and successively carried out by several other groups, has revolutionised this concept. These studies show that angiogenesis, the fundamental process leading to the formation of new blood vessels by sprouting from pre-existing endothelium, is stimulated by tumour cells, and that it is of critical importance in the processes of tumour invasiveness, progression and metastasis [10].

It is now assumed that carcinogenesis and tumour progression

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