Prodrugs in cancer chemotherapy

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Many drugs used in cancer chemotherapy are general cytotoxic agents and do not have any specific activity towards tumour cells. The aim of the medicinal chemist working in this field is therefore to design structures which will exploit the minor differences between normal and neoplastic cells, as and when they are described by the biochemist. The pharmacologist is also involved in describing the metabolism of the drug and the distribution and persistence of the active metabolite. However, it is only when it has been fully tested for anti-tumour activity and toxicity, and proceeds into clinical evaluation, that a drug’s true worth can be ascertained. The development of a new drug from its inception until the time when it is accepted clinically, involves the skills and interaction of numerous disciplines. The availability of such interactions is vital if the maximum effectiveness is to be achieved from any drug type.

Drug design often involves some form of prodrug, or latently active compound, i.e. a chemical which is not itself active, but which requires conversion to its active form after administration. Two classes of prodrug can be defined, one requiring biological modification leading to an active metabolite and the other undergoing chemical decomposition to an active metabolite. Whilst many prodrugs are arrived at by design, many have been discovered by chance, or proved to be active by a mechanism other than that originally intended. This is particularly true in the field of cancer chemotherapy. Few specifically designed prodrugs have found clinical utility as anti-tumour agents, whilst others, which were not designed as such but have subsequently proved to be prodrugs, enjoy widespread application.

The sites and mechanisms of the prodrugs requiring biological activation vary widely and may for the purposes of this discussion be subdivided into two groups. One, currently by far the largest, is of drugs requiring activation by general metabolic enzymes. Examples of this group of prodrugs are the hepatic oxidation of cyclophosphamide, dacarbazine and hexamethylmelamine, and the phosphorylation of the purine and pyrimidine anti-metabolites, which require conversion to a nucleotide form before they can exert their cytotoxic effects. The second group would then be those compounds which exploit an enzyme specific to the tumour to release the active species in situ, e.g. the azomustards and $\gamma$-glutamyl and plasmin derivatives. To date, most prodrugs in cancer chemotherapy fall into the former category, but increasingly attempts are being made to design specific tumour-activated prodrugs. The simple cataloging of prodrugs designed for use as cancer chemotherapeutic drugs is unlikely to prove instructive, but lessons can perhaps be learnt from the study of some individual cases drawn from each category, in particular the need for the multidisciplinary approach.

To begin with then, probably the most widely used and valuable alkylating agent in clinical practice, cyclophosphamide (I), synthesized in 1958 (Arnold & Bourseaux, 1958), was designed to be activated by a phosphoramidase (Fig. 1), which was expected to cleave the N-P bond, liberating the active alkylating agent nor-nitrogen mustard (II) at sites where this enzyme is abundant (at that time believed to include tumour cells). However, cyclophosphamide subsequently proved not to be a substrate for this enzyme, but to be activated by a different mechanism. The presently accepted metabolism of cyclophosphamide is also illustrated in Fig. 1. This metabolic route is initiated in the liver by the mixed-function oxidase system, an enzyme system which, it will be seen, is involved in the activation of many anti-tumour prodrugs.

In the case of cyclophosphamide, initial oxidation occurs at the 4-position of the oxazaphosphorine ring, the position adjacent to the ring nitrogen, to form the hydroxylated derivative (III). 4-Hydroxycyclophosphamide (III) undergoes a series of chemical breakdowns, which eventually result in the formation of the active metabolite phosphoramidine mustard (IV). Alternative pathways involving further biological oxidation lead to inactive metabolites (Struck et al., 1971).

In addition to phosphoramidine mustard, the other biologically significant metabolite is acrolein (V). This compound is also cytotoxic (Cox et al., 1976), but is believed to be responsible for the toxic side-effects of cyclophosphamide, in particular haemorrhagic cystitis (Brock et al., 1979), rather than for any of its anti-tumour properties. This was elegantly confirmed by Cox (1979), who showed that bladder toxicity in rats was caused by the analogue of cyclophosphamide in which the chloroethyl groups were replaced by ethyl groups, in the same way as by cyclophosphamide. This same analogue was shown to be metabolized similarly to cyclophosphamide, in that it produces acrolein but no other cytotoxic species.

Attempts to design alternative prodrug analogues of cyclophosphamide which would produce less toxic metabolites than acrolein, whilst retaining the anti-tumour activity of the phosphoramidine mustard metabolite, have been made. In general, these have not proved sufficiently successful to awaken clinical interest. However, the other derivatives of 4-hydroxycyclophosphamide have done so. In this case no oxidative metabolism is required because such compounds are inherently chemically unstable. One of these, ASTA Z7557 (VI), is stable at pH 4, but hydrolyses rapidly to an active alkylating agent at pH 7. This results in good anti-tumour activity, and the compound does not lead to bladder toxicity. Clinical trials with this agent are currently in progress.

Oxidative metabolism at the carbon adjacent to a
nitrogen atom is required for the activation of a number of other anti-tumour agents. These include in particular 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (dacarbazine DTIC), hexamethylmelamine and procarbazine, the first two of which will be considered in more detail.

The triazenes, or rather DTIC (VII) was one of the first clinically useful anti-tumour drugs to be devised as a prodrug, but inevitably its actual mode of action proved to be different from that expected. DTIC was designed by Shealy and his colleagues to be a prodrug form of 5-diazoimidazole-4-carboxamide (VIII), a chemically unstable inhibitor of the Walker 256 carcinosarcoma (Shealy et al., 1961, 1962a,b). However, the decomposition of DTIC to this anticipated cytotoxic product only occurs under certain photochemical conditions (Fig. 2), and is not related to its anti-neoplastic activity. Although not working by the originally intended mechanism, DTIC has proved of value clinically (Carter & Friedman, 1972). Its most significant single agent activity is in
producing a 23% response rate in the treatment of malignant melanoma (Comis & Carter, 1974), the highest response rate produced in this disease by any single agent (Lucas & Huang, 1982). Subsequent investigations have demonstrated that DTIC is still a prodrug although by a different mode of activation (Fig. 2). Oxidative metabolism in the liver gives rise to the N-hydroxymethyl analogue [IX; 5-(3-hydroxymethyl-3-methyl-1-triazeno)imidazole-4-carboxamide, HMIC], which undergoes chemical loss of formaldehyde to form the monomethyl derivative [X; 5-(3-methyl-1-triazeno)imidazole-4-carboxamide, MTIC]. MTIC is also chemically unstable, and after rearrangement, produces a methylating species, either a methyl diazonium species or a methyl carbonium ion. In particular, oxidative N-demethylation of DTIC has been shown to occur in vivo, by identification of HMIC and MTIC in the plasma of treated mice, rats and patients (Rutty et al., 1983).

The peak plasma level of HMIC attained in the rat (2.0 m) is reduced some 14-fold as compared with the mouse (27.5 m); that of MTIC is undetectable in the rat and 6.4 m in the mouse. This poor activation of DTIC in the rat is reflected in its low activity against the Walker 256 carcinosarcoma. The limited clinical activity of DTIC also appears to be a consequence of its inadequate metabolism. In a group of seven patients, the mean peak plasma level of HMIC and MTIC were 2.3 m and 4.7 m respectively. DTIC would seem therefore to be a prodrug, which is poorly activated by man, whereas this process takes place much more efficiently in the mouse. Such species differences in metabolism are a major problem in the use of animal models for drug testing and must be born in mind when designing prodrugs for use in man. A similar situation will be encountered in the discussion of the methylmelamines.

The poor metabolic activation and the consequent poor clinical activity of DTIC have resulted in a search for a second-generation analogue. This was initiated with a structure–activity study by Connors et al. (1976), who demonstrated the minimal requirements for anti-tumour activity of the triazenes (Fig. 3). The carrying structure at N-1 may be aryl or heteroaryl, the methyl group at N-3 is an absolute requirement, and the other substituent at N-3 must be a proton or a group readily lost by metabolism. In the case of linear alkyl substituents at N-3 in the aryl series, activity decreases with groups larger than pentyl (Wilman et al., 1984).

The metabolism and anti-tumour activity of the aryl-triazenes is similar to that of DTIC but exhibits slightly modified species differences in respect of the oxidative metabolism (Rutty et al., 1984). Examination of the pharmacokinetics and metabolism of 1-(4-carbamoylphenyl)-3,3-dimethyltriazenes (XI; CB-10-286) in the mouse showed it to be readily metabolized and to produce four-fold greater plasma levels of the monomethyl metabolite 3-(4-carbamoylphenyl)-1-methyltriazenes. (XII; CB-10-347), than in the rat. Overall the aryltriazenes yields much higher levels of its cytotoxic monomethyl metabolite than does DTIC, especially in the rat.

The anticipated difficulties involved in the formulation of a drug as lipophilic as CB 10-286, log P = 1.2 (Wilman et al., 1984), have resulted in the choice of the analogous 4-carboxyphenyl derivative, 1-(4-carboxyphenyl)-3,3-dimethyltriazenes (XIII; CB10-277), as a potential clinical alternative to DTIC.

Originally, in addition to DTIC, 5-[3,3-bis-(2-chloroethyl)-1-triazeno]imidazole-4-carboxamide (XIV; BTIC) was investigated clinically. However, despite being the more active drug against the L1210 leukaemia, it was not as effective in man. Metabolism of BTIC (Fig. 4) parallels that of DTIC in leading to a monoalkyl, in this case a 2-chloroethyltriazenyl (XV; MCTIC; Shealy, 1975). A second series of compounds designed as chemically activated prodrug forms of these two cytotoxic imidazole derivatives has been pursued by Stevens and his colleagues at the University of Aston. The first of these compounds, 8-carbamoyl-3-(2-chloroethylimidazo[5,1-d]-1,2,3,5-tetrazin-4(4H)-one (XVI; mitozolamide), cures many experimental tumours (Hickman et al., 1985). It has been shown to decompose chemically, under mildly alkaline conditions, by opening of the tetrizene ring, to yield MCTIC (Stevens et al., 1984). Biological evaluation of mitozolamide also points to the drug acting as a prodrug form of MCTIC (Stevens, 1986).

The phase I clinical study of mitozolamide (Newlands et al., 1985) covered doses from 8 to 153 mg/m² and demonstrated dose-related but not severe vomiting, with thrombocytopenia as the dose-limiting toxic effect at doses greater than 115 mg/m². The plasma half-life of the drug was 1–1.3 h and independent of the route of administration (intravenous or oral). Partial responses were seen in two patients with adenocarcinoma of the ovary who had received previous cisplatin therapy. Phase II studies with this drug are planned against melanoma and lung and ovarian tumours.

A detailed structure–activity study (Langdon et al., 1985a; Stevens, 1986) has indicated the structural requirements for anti-tumour activity in this class of compounds (Fig. 5). The nature of the substituent groups required are: R¹, amide, sulphonamide, sulphone or sulphoxide; R², hydrogen or small alkyl; and R³, chloroethyl or methyl. Anti-tumour evaluation of these compounds has indicated that the most active is 8-carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(4H)-one (XVII; CCRG 81045). This compound decomposes chemically in a similar fashion to mitozolamide, in this case producing MTIC as the active metabolite, the presumed active metabolite of DTIC, without the need for biological activation (Fig. 6). Extensive testing of CCRG 81045 in experimental tumour systems has shown it to be superior to DTIC and to have a different spectrum of activity to
mitozolamide (Langdon et al., 1985b). Consequently, it has been selected for toxicological evaluation before phase I clinical trial (Stevens, 1986).

In the case of both cyclophosphamide and DTIC, oxidative metabolism at the a-carbon is followed by chemical loss of an alkyl aldehyde to produce the active species. For the methylmelamines, on the other hand, it is the primary oxidation product, the N-hydroxymethyl derivative, which is believed to be responsible for the cytotoxic effect.

The methylmelamines are once again a group of compounds which have proved to be prodrugs subsequent to their introduction into clinical practice. The anti-tumour activity of hexamethylmelamine (XVIII; HMM), the initial clinical agent in this series, was discovered independently by Buckley et al. (1950) and by Hendry et al. (1951). Despite the fact that its activity against the standard rodent tumours is at best marginal, it was introduced into the clinic (Wilson & de la Garza, 1965) and has proved to have a wide spectrum of moderate activity against solid tumours (Legha et al., 1976). Activity is most marked against ovarian cancer, lymphomas and carcinoma of the cervix, and to a lesser extent bronchogenic and breast carcinomas.

Initial theories concerning the mechanism of action of HMM notes its similarity to triethylenemelamine (TEM) and suggested that its role was that of an alkylating agent. However, the fact that it fails to react with 4-((p-nitrobenzyl)pyridine shows this not to be the case. Moreover, its metabolism differs markedly from TEM (Worzalla et al., 1973). Indeed it was originally synthesized as a non-alkylating analogue of TEM (Hendry et al., 1951). A number of early reports on the metabolism of HMM in relation to its anti-tumour activity (Worzalla et al., 1973, 1974; Lake et al., 1975) indicated that enzymic oxidative demethylation led to the production of a series of lower homologues. Much recent work in relation to the metabolism and mechanism of action of the methylmelamines has been undertaken by Rutty and her colleagues. These studies have been intimately involved with our search for second and third generation analogues of HMM.

HMM has two major disadvantages from the clinical point of view. It is extremely insoluble in aqueous media and is therefore not suitable for intravenous administration, and has of necessity always been administered orally. The second clinical problem is the severe nausea and vomiting encountered in all patients. The necessity for oral administration meant that it was not possible to determine whether this toxicity was a local or centrally mediated effect, as the dose-limiting toxicity is neurological together with some myelosuppression.

The search for a suitable second-generation methylmelamine therefore centred on compounds with at least the same anti-tumour activity as HMM, but also increased aqueous solubility to facilitate parenteral administration. The design of such a compound was hindered by the lack of a sufficiently sensitive test system. Only one rodent tumour, the mouse ADJ/PC6A plasmacytoma, shows any significant response, but even in this system the activity of HMM is in no way comparable with that of other agents to which the tumour is sensitive, difunctional alkylating agents such as melphalan for example.
This problem was fortuitously overcome when it was found that certain human tumour xenografts were particularly sensitive to HMM (Mitchley et al., 1975). One of these, a human lung adenocarcinoma (P246) growing originally in immune-deprived mice and latterly in athymic nude mice, was chosen for a structure–activity study initiated by Ross and co-workers (Connors et al., 1977; Cumber & Ross, 1977; Mitchley et al., 1977). All the analogues in this study were designed to have greater water solubility than HMM and three had equal or greater anti-tumour activity. These were N-hydroxymethylpentamethylmelamine (XIX), pentamethylmelamine (XX) and sym-trihydroxymethyltrimethylmelamine (XXI; trimelamol).

Fig. 7. Metabolism of HMM (XVIII)

Metabolic studies (Fig. 7) have shown that HMM (XVIII) undergoes oxidative metabolism to N-hydroxymethylpentamethylmelamine (XIX), which by chemical loss of formaldehyde forms pentamethylmelamine (XX). Further metabolism results in progressive symmetrical loss of the remaining methyl groups, in a similar fashion. As the N-hydroxymethylmelamines are inherently unstable, pentamethylmelamine was chosen for phase I clinical trial.

Phase I trials were undertaken in a number of centres, all of which failed to demonstrate any significant activity even at severely toxic dose levels. The major side effect was gastrointestinal, i.e. dose-related nausea and vomiting (Muindi et al., 1983), indicating that this is not a local effect but mediated via the central nervous system. This is supported by the occurrence of other neurological effects at very high doses. The associated pharmacokinetic studies have provided an insight into the possible reasons for the lack of tumour inhibition (Rutty et al., 1982; Muindi et al., 1983).

There is a major difference in the rate of metabolism of the methylmelamines between the mouse, rat and man (Rutty et al., 1985). In the mouse the metabolism of pentamethylmelamine is more rapid (plasma $t_{1/2} < 15$ min) than the rat (plasma $t_{1/2} = 40$ min), and quicker in both than in man (plasma $t_{1/2} = 102$ min). Additionally the peak plasma concentration of cytotoxic N-hydroxymethylmelamines, the primary oxidative metabolites of the methylmelamines, are correspondingly higher in the mouse than in the rat, whilst in man they are undetectable. These differences are paralleled by the anti-tumour activity of HMM and pentamethylmelamine, which are active in murine tumour systems, much less active against rat tumours and have poor or no activity in man. Rutty et al. (1982) therefore concluded that, because of the highly cytotoxic nature of the N-hydroxyethylmelamines, the relative anti-tumour effectiveness of pentamethylmelamine between mouse, rat and man may well be related to the metabolic and pharmacokinetic differences.

It would therefore seem that in order to achieve the full clinical potential of compounds of this type, it will be necessary to adapt the drug in an active form, i.e. to remove the requirement for oxidative metabolism. Thus the methylmelamines would appear to be a case where the use of a prodrug form is not suitable.

The structure–activity study from which pentamethylmelamine was developed also produced two N-hydroxymethylmelamines, with equal experimental anti-tumour activity and sufficient solubility for systemic administration (Connors et al., 1977). It had originally been thought that such compounds would not be sufficiently stable to allow a suitable formulation to be achieved; however, this has proved to be untrue in the case of trimelamol.

Trimelamol has the additional advantage of being 10 times more cytotoxic to tumour cells in vitro compared with pentamethylmelamine (Rutty & Abel, 1980), and in the rat it produces plasma levels of N-hydroxymethylmelamines comparable with those achieved in the mouse after pentamethylmelamine administration (Newell et al., 1981). As a result of these observations trimelamol has undergone clinical investigation as a potential third-generation melamine.

The phase I study has demonstrated trimelamol to be a drug worthy of further study. Dose-related vomiting was much less than that observed with other methylmelamines and no acute sedation was seen, as was expected from its reduced penetration into the brains of mice. The dose-limiting toxicity was myelosuppression particularly leukopenia. Responses were observed in carcinoma of the ovary and rectum and in Hodgkin’s disease (Judson et al., 1985).

Ideally, the activation of a prodrug should be restricted to its required site of action. Although this is not always possible, it must be the aim of the medicinal chemist. Connors (1978) has suggested a number of criteria which must be born in mind in drug design, if improved selectivity in vivo is to result from site-specific activation. Originally constructed with alkylating agents in mind, such criteria are obviously applicable in all fields.

(1) The prodrug must be considerably less toxic than the active species.

(2) The model system, and subsequently the tumours investigated clinically, must be shown to contain the activating enzyme, and this should be absent or in much lower concentration in all normal host tissue.
and his colleagues to the synthesis of the nitrogen mustard derivative which would be specific for primary tumours occur widely in parts of Africa and the Far East (Higginson, 1970). This is in contrast to the primary liver tumours seen in Europe and the U.S.A., which grow much more slowly. The azo mustard derivative 4-[N,N-bis(2-chloroethyl)amino]-2'-carboxy-2-methylazobenzene (XXVII, R = CH₂, X = Br; CB 10-252) was designed as a prodrug form of a very reactive phenylenediamine mustard, which would be selectively activated in such tissues containing the appropriate enzyme system. The rapid hydrolysis of the metabolite prevents its toxic effects from spreading to other proliferating tissues.

The ability to reduce the azo compounds was later shown to be a property of primary hepatocellular carcinoma (Autrup et al., 1974). CB 1414 therefore fulfilled some of Connors’ criteria for a drug to be truly tumour selective, i.e. it is inactive itself, but capable of metabolism to a potent cytotoxic agent by a rapidly proliferating tumour. The requirement that the toxic metabolite should remain within the confines of the tumour, is more difficult to achieve. However, investigation of a further series of azo mustards containing various alkylating functions and their corresponding phenylenediamine derivatives, by Bukhari et al. (1973), produced a drug, CB 10-252, with an alkylating metabolite, 4-bis(2-bromo-n-propyl)aminomethyl-2-methylaniline (XXIV, R = CH₃, X = Br), which has a half-life of only 41 s at pH 7.5 and 37°C. Thus the parent azo compound, CB 10-252, is a virtually non-toxic drug, which is reduced to a very toxic metabolite in tissues containing the appropriate enzyme system. Confirmation of this selectivity was produced by Connors et al. (1973). When the Walker 256 tumour was implanted in the liver of rats it was more susceptible to the action of CB 10-252 than to cyclophosphamide, whereas when the tumour was implanted in the flank the reverse was true.

(3) The prodrug must be a suitable substrate for the enzyme under physiological conditions.

(4) The activated species must have a short biological half-life so that the toxic effects are limited to the tumour, and selectivity is not lost by diffusion of activated drug away from the tumour.

Similar criteria had originally been applied by Connors and his colleagues to the synthesis of the nitrogen mustard derivative which would be specific for primary hepatocellular carcinoma. These rapidly proliferating tumours occur widely in parts of Africa and the Far East (Higginson, 1970). This is in contrast to the primary liver tumours seen in Europe and the U.S.A., which grow much more slowly. The azo mustard derivative 4-[N,N-bis(2-bromo-n-propyl)amino]-2-carboxy-2-methylazobenzene (XXII, R = CH₂, X = Br; CB 10-252) was designed as a prodrug form of a very reactive phenylenediamine mustard, which would be selectively activated in such tumours.

Ross & Warwick (1955, 1956) had shown that because of their highly conjugated structure, nitrogen mustards of this type (XXIII) tend to be chemically unreactive and therefore non-toxic. After enzymic reduction of the azo group, two metabolites are formed (Fig. 8), an aniline derivative (XXXIII) and a p-phenylenediamine derivative (XXIV) (Ross & Warwick, 1956; Bukhari et al., 1973). Ross & Warwick (1956) further showed that this reduction occurs both chemically in the presence of hydrazine and enzymically under the influence of the xanthine-xanthine oxidase system. In particular, they found a striking correlation between reducibility and anti-tumour activity against the Walker 256 rat carcinoma. This investigation also showed that a carboxylic acid group ortho to the azo group is necessary for activity.

The most active compound of this early series was 4-[N,N-bis(2-chloroethyl)amino]-2-carboxy-2-methylazobenzene (XXII, R = H, X = Cl; CB 1414). This compound underwent clinical trial (Israels & Ritzmann, 1960), but was devoid of significant benefit; however, it should be noted that liver tumours were not investigated.

Some 15 years later, Connors et al. (1972) confirmed that the enzyme system required for the reductive cleavage
Shortly after its development, CB 10-252 was tested briefly in Nairobi, Kenya; however, although encouraging results were obtained (Autrup & Warwick, 1975) the investigation was not persued. A British trial (Murray-Lyon et al., 1978) against primary hepatocellular carcinoma showed no tumour regression, but, as was indicated earlier, there is a marked difference in proliferation rate between this and the African type of tumour. The myelo-suppression encountered in this trial may be explained by the results of Kitamura & Tatsumi (1983), who demonstrated that the enzyme aldehyde oxidase is also capable of reducing the azo bond.

This azo bond is one of the few cases where the prodrug form of an alkylating agent has proved to be active in the way predicted.

Aniline mustard [XXV; bis-(2-chloroethyl)aniline] was the first aromatic nitrogen mustard to be synthesized (Robinson & Watt, 1934), although it was not until later (Ross, 1949) that its preparation was directed towards cancer chemotherapy. It was later still before its mechanism of action was investigated and today it awaits the exploitation of its apparent clinical potential.

Connors & Whisson (1965, 1966) demonstrated that aniline mustard is first metabolized in the liver (Fig. 9) to 4-hydroxyaniline mustard (XXVI) and subsequently rapidly conjugated to form the O-glucuronide (XXVII). Tumours with high levels of the enzyme β-glucuronidase have the ability to cleave this conjugate to release the extremely cytotoxic 4-hydroxyaniline mustard. Synthesis and testing of various glucuronic acid derivatives in the mouse ADJ/PC6A tumour system gave added support to this theory (Bukhari et al., 1972).

Young et al. (1976) have reported a significant clinical trial with aniline mustard. In this trial, an attempt was made for the first time to compare the activity of the drug with the β-glucuronidase levels of some of the tumours. Although only six of the 78 patients with advanced tumours who were treated showed any response, some correlation was seen with the enzyme level. In particular, two tumours with initially high levels of β-glucuronidase were sensitive to treatment with aniline mustard. However, on relapse they were found to be both insensitive to the drug and to lack the enzyme.

Aniline mustard would therefore seem to be established as a prodrug of 4-hydroxyaniline mustard, albeit by a roundabout route. However, to date no clinical trial has taken place limited solely to those tumours which have been biochemically shown to contain β-glucuronidase. It is therefore currently impossible to determine the true clinical worth of this drug.

Solid tumours, even when quite small, may develop ischaemic regions of mainly necrotic tissue (Goldacre & Whisson, 1966). These areas are surrounded by viable cells existing under oxygen-deficient, or hypoxic, conditions. Outwards from this layer are the only well-vascularized areas of the tumour. The hypoxic regions have long been recognized as a problem in radiotherapy, and they may also limit the effectiveness of chemotherapy, either by reduced uptake from the poor blood supply, or because they are non-proliferative and therefore not sensitive. However, attempts to exploit this potential reducing environment may be thwarted, as the anaerobic bacteria in the gut are very capable of undertaking similar reductions, in an area of sensitive tissue.

Use has been made of, so called, radiosensitizing drugs in an attempt to overcome the radiotherapeutic problem of low oxygen levels in the centre of large tumour masses. These compounds, in the main nitroimidazole derivatives, are reduced in the hypoxic areas via free-radical and other reactive species, which may be involved in their mechanism of action.

Many cytotoxic agents have a requirement for reduction. In particular, the quinone-containing antibiotics, such as adriamycin, daunomycin and mitomycin C, require reduction to the hydroquinone form as the first stage of activation.

As tumour tissue, due to its metabolic differences, has a somewhat higher reducing capacity than normal tissue (Cater & Phillips, 1954), it may lead to preferential activation of such drugs. The design of drugs to make use of this property has given rise to the concept of bioreductive activation. This concept has been extensively employed by Sartorelli and his colleagues (Lin et al., 1972 et sequela) to design benzozquinones, naphthoquinones, quinoline-quinones and naphthazarines that are mono- and di-substituted with CH2-X (where X becomes a leaving group, after reduction of the quinone). Many of these compounds have anti-tumour activity in vivo.

Finally, a new compound with a completely novel structure and specificity from the point of view of anti-tumour agents. Ipomeanol [XXVIII; 1-(3-furanyl)-4-hydroxy-1-pentanone] is currently being developed in the U.S.A., by the National Cancer Institute. It exhibits its cytotoxicity after oxidation of the 4-hydroxy group to keto by cytochrome P-450 (Fig. 10). The unique feature of ipomeanol, however, is that this oxidation only occurs in Clara cells (Narayanan, 1986). It is therefore to be hoped that this compound will be of use in the treatment of lung tumours derived from such cells.


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