The End of Cytotoxics?

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Abstract

Cytotoxic drugs were the first form of cancer chemotherapy to be established, but they can have quite severe side effects. Cytotoxics attack all rapidly dividing cells, including healthy cells and cancer cells. They can therefore cause side effects such as loss of hair, damage to the skin and mucosa, and damage to bone marrow, affecting the immune system. For this reason, the focus of some cancer research has moved from cytotoxics to targeted therapeutics, including monoclonal antibodies. Monoclonal antibodies can be very effective in patients who express the appropriate target; however, not all patients do, and some develop resistance. Monoclonal antibodies, like other biologicals, are also very costly. All is not lost for cytotoxics. Because they have been around for so long, there is an abundance of data on their modes of action. Based on these data, researchers have developed newer cytotoxics that are more effective and have fewer side effects, and approaches that deliver cytotoxics more safely or target them to tumours.

Keywords

Antigens, cancer, cytotoxics, drug delivery, monoclonal antibodies, targeting

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Cancer is characterised by uncontrolled and unlimited multiplication of cells outpacing the natural rate of cell death (apoptosis).[1] The treatment of cancer involves cytotoxic or targeted therapeutics that kill the cancer cells, stop their multiplication, inhibit metastasis or break tolerance against cancer cells by modulating T-regulatory cells or antigen-presenting/T-cell recognition via vaccination (see *Figure 1*).

According to the WHO, cancer is one of the leading causes of death worldwide. There were around 7.4 million deaths from cancer in 2004, predicted to rise to around 12 million in 2030.[2] This increase is driven by an ageing population, rising levels of obesity and the increasing use of tobacco and alcohol in both the developing and the developed world. The treatment of cancer is therefore a growing market. The market value was around US$50 billion in 2009, an increase of about 8 % on 2008, and about 40 % of this represented US sales.[3]

What are Cytotoxic Drugs?

Cytotoxic drugs were the first form of cancer chemotherapy to be established. They act by destroying rapidly dividing cells. The earliest use of cytotoxics can be traced back to nitrogen mustard, which was used to treat squamous cell carcinoma.[1] Nitrogen mustard was derived from mustard gas and developed (but never used) as a poisonous gas in World War I. It is thought that it was first used to treat cancer as early as 1942. In results published in 1946, patients with haematopoietic disorders, including Hodgkin's disease, lymphosarcoma and leukaemia, showed improvements after treatment with nitrogen mustard; some were even able to go back to work. Nitrogen mustard was most effective in treating Hodgkin's disease, with one patient showing a good response for 33 months.[4–6]

Cytotoxic drugs have been used for many years and most physicians are used to handling them. There is a large amount of data on their safety and efficacy, and a wide range of combination regimens for many different types of cancers. These drugs also tend to be low-cost because many of them are available in generic forms.

The main groups of cytotoxic drugs are:

- alkylating agents;
- topoisomerase inhibitors;
- anthracyclines and other cytotoxic antibiotics;
- antimetabolites; and
- antimicrotubule or antitubulin agents.

This first section of the article provides a brief introduction on the action of the different types of cytotoxic agents.

Alkylating Agents

Alkylating agents are the most widely used cytotoxic drugs and they target the DNA in cancer cells. They include the nitrogen mustards and platinum-based drugs, which are used in more than 50 % of combination treatment regimens.[7] The other key groups of alkylating agents are the aziridines, alkyl sulphonates and nitrosoureas.[1]

Alkylating agents covalently bond with DNA strands, preventing DNA replication and potentially limiting RNA replication and protein production. Bifunctional alkylating agents cross-link between DNA strands (inter-strand) or within DNA strands (intra-strand); monofunctional alkylating agents do not form cross links. Once the DNA is damaged, this inhibits cell-cycle progression and either the cell dies or

the DNA is repaired. Enhanced ability to repair DNA cross links in tumour cells may explain the development of resistance to alkylating agents.[1]

The most widely used alkylating agents include the nitrogen mustards cyclophosphamide and ifosfamide, which have bifunctional alkylating metabolites.[8] The platinum-based agent cisplatin was first assessed as an antitumour agent in 1969. Cisplatin forms DNA adducts, leading to cell death, but its mechanism of action is still not clear.[9] Aziridines, such as thiotepa and mitomycin C, are activated by enzymes and form inter-strand cross links.[1] Busulphan is a widely used example of the alkyl sulphonates, and forms inter-strand cross links, as does the nitrosourea carmustine.[1]

Topoisomerase Inhibitors

Topoisomerase inhibitors wind and unwind DNA during DNA replication and protein synthesis, and inhibiting these enzymes leads to cell death. For example, topoisomerase II induces transient double-strand breaks during DNA replication and transcription, and then catalyses strand break repair. Inhibiting topoisomerase II prevents the strand break repair, leading to programmed cell death.[10] For example, the topoisomerase II inhibitor etoposide acts by stabilising the DNA–topoisomerase II complex.[11]

Topoisomerase I inhibitors, such as camptothecin and camptothecin derivatives, inhibit the relegation stage of the nicking–closing reaction catalysed by topoisomerase I, leaving the enzyme covalently complexed with DNA.[11]

Anthracyclines and Other Cytotoxic Antibiotics

The earliest antitumour antibiotic, actinomycin A, dates back to the 1930s. Actinomycin A was isolated from *Streptomyces*. Anthracycline antibiotics have a number of targets in the cell. They bind to DNA and intercalate in the major groove of the double helix, which may cause the double helix to unwind by separating purine and pyrimidine bases. They also bind to RNA, proteins and lipids, interfering with the replication of DNA, the transcription and translation of DNA, and inhibiting enzymes and affecting membrane function.[10]

Anthracycline antibiotics also inhibit topoisomerase II, which induces transient double-strand breaks during DNA replication and transcription, and then catalyses strand break repair. Inhibiting topoisomerase II prevents strand break repair, leading to programmed cell death.[10]

Anthracenedione antibiotics such as mitoxantrone intercalate into the double helix and act as topoisomerase II inhibitors.[10] Actinomycins, for example actinomycin D, intercalate between base pairs in DNA and lie in the minor groove of DNA. Actinomycin D forms a very stable complex with single- and double-stranded DNA, inhibiting RNA and protein synthesis.[10] Mitomycin C forms DNA inter-strand cross links and inhibits DNA replication, and the bleomycins cause fragmentation of DNA.[10]

Antimetabolites

Antimetabolites prevent cell division by being incorporated into nuclear material or by combining with cellular enzymes.[12] Antimetabolites include pyrimidine antimetabolites, such as fluorouracil (5-FU), which inhibit the enzyme thymidine synthase and are incorporated into RNA.[8] Antifolates affect the production of folate compounds and thus inhibit the folate-dependent enzymes required for DNA synthesis. An example is methotrexate, the most widely used antifolate, which is an inhibitor of dihydrofolate reductase, part of the DNA synthesis pathway.[8]

Figure 1: Approaches to Treating Cancer

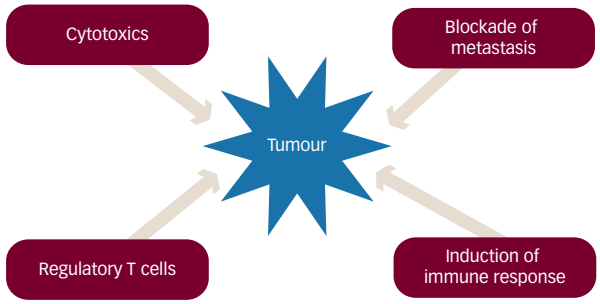


Table 1: Side Effects Associated with Cytotoxic Agents

Cytotoxic Agent	Side Effect
Alkylating agents	Increased risk of acute non-lymphocytic leukaemia[12]
Anthracyclines, taxanes and bleomycin	Accumulation can lead to severe side effects, thus need for setting a 'lifetime dose'[8,13]
Anthracyclines	• Acute and chronic cardiotoxicity[12] • Carcinogenicity/mutagenicity
Vinca alkaloids	Neurotoxicities such as peripheral or autonomic neuropathy[12]
Taxanes	• Hypersensitivity reactions[14] • Neuropathy[14]
Platinum-based compounds	Nephrotoxicity[7]
Antifolates	Acute renal failure[8]

Antimicrotubule or Antitubulin Agents

The taxanes and vinca alkaloids act by disrupting the assembly of microtubules, which are involved in cytokinesis, mitosis and vesicular transport.[8]

Paclitaxel was the first taxane on the market, and was isolated from the bark of the Pacific yew tree *Taxus brevifolia*. Taxanes interrupt cell division and cause cell cycle arrest.[8] Docetaxel is a semi-synthetic analogue of paclitaxel.

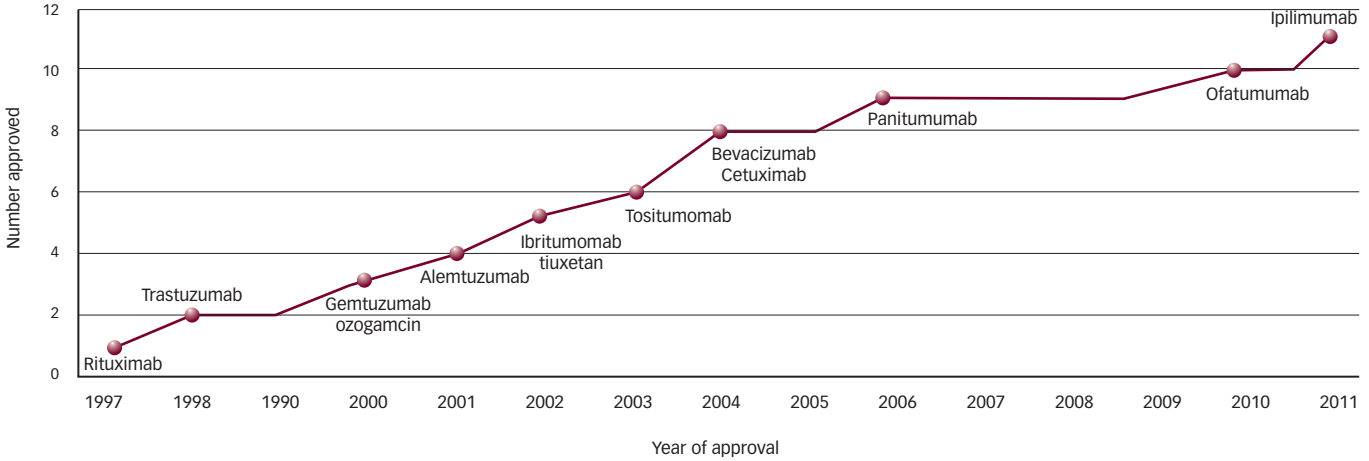
The original vinca alkaloids, vincristine and vinblastine, were isolated from *Vinca rosea L*, the periwinkle plant. These vinca alkaloids interfere with the balance between tubulin and microtubules and prevent mitosis, which triggers apoptosis.[8] Follow-up vinca alkaloids include vindesine and vinorelbine.

Disadvantages of Cytotoxic Agents

Cytotoxic agents are associated with toxicity because of their mode of action. Cytotoxics attack all rapidly dividing cells, including healthy cells and cancer cells, and so they can cause side effects by damaging normal rapidly dividing cells. This causes hair loss, damage to skin and mucosa (which can lead to nausea, vomiting and diarrhoea), anorexia, fever, and damage to bone marrow, affecting the immune system (myelosuppression). Cytotoxics can damage vascular tissue if they leak into the extravascular compartment, causing tissue necrosis and requiring tissue grafting.[10,12] Men undergoing chemotherapy are often advised to bank sperm before treatment because of the effect on sperm, which also divide rapidly.[10]

Different types of cytotoxic agents can also cause specific side effects. For examples of such side effects, see *Table 1*.[7,8,12,13,14]

Figure 2: Monoclonal Antibodies for Cancer Therapy Approved by the US Food and Drug Administration



Sources: MD Becker Partners, 2010;[20] Davis, 2011.[21]

Targeted Therapies – Is this the End of Cytotoxics?

In the 40 years since 1971, when President Nixon announced a war on cancer, the cumulative adult death rate from cancer (adjusted for the size and age of the population) has fallen by less than 5 % despite investments of over US$100 billion.[15] Cytotoxics have been the mainstay of the cancer therapeutics market during that period, but their high toxicity profile and their lack of impact on the death rate have left an opening for a new generation of therapeutics.

There has been a huge growth in the identification and validation of specific tumour targets, particularly through the explosion of the genomic data available. Researchers have responded to this by developing targeted therapeutics, including monoclonal antibodies.

The rationale behind targeted therapeutics is that they home in on specific biomarkers on diseased cells, maximising therapeutic benefit and minimising the effects on healthy cells.[16] Targeted therapeutics can be used as monotherapies or combination therapies with other biologicals or with cytotoxic agents.[17]

One of the key focuses of research into targeted therapies is the development of monoclonal antibodies. Antibodies are designed to target protein biomarkers on the surface of bacteria and viruses and destroy them. The development of monoclonal antibodies harnesses this action so that they target specific protein markers on the surface of target cells.

According to a 2010 analysis by Nelson et al., cancer and immunological disorders are the main therapeutic areas for monoclonal antibody research, but the approval rate is lower (around half) for monoclonal antibodies for oncology compared with immunology.[18]

In 2009, about 30 % of the sales of the top 10 oncology products were monoclonal antibodies[3] and the biological therapeutics market overall is likely to be worth US$53 billion by 2014,[8] with a growth rate of around 7 %.[19] The number of monoclonal antibodies approved for launch has grown since 1997 (see *Figure 2*).[20,21]

Mechanism of Action of Monoclonal Antibodies

Monoclonal antibodies have a number of different mechanisms of action. Once they have bound to cancer cells they can activate antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, triggering the immune system to destroy the cells. Monoclonal antibodies can also be designed to target the growth factors that tumour cells require for growth and development, such as vascular endothelial growth factor (VEGF). For example, bevacizumab targets VEGF, blocking angiogenesis, and is used to treat a range of cancers.[22]

Monoclonal antibodies have also been developed to target growth factor receptors, such as the epidermal growth factor receptor (EGFR) family. For example, trastuzumab targets the EGFR human epidermal growth factor receptor 2 (HER2) and is effective in HER2-positive breast cancers; cetuximab targets EGFR, inhibits its activation and is used in colorectal and head and neck cancer.[22] Monoclonal antibodies also use a range of other actions, including triggering apoptosis.[22]

Disadvantages of Targeted Therapies

The early monoclonal antibodies were murine and caused problems with immunogenicity, which affected both safety and efficacy. The side effects of monoclonal antibodies are generally just a flu-like response, such as mild-to-moderate fever and chills, or an injection site reaction, and these generally improve after the first administration. Some people may develop an anaphylactic reaction. This is a hypersensitivity antigen-antibody reaction that can develop three to four hours after administration and may be fatal.[23] Immune responses to monoclonal antibodies can also affect efficacy by reducing therapeutic antibody serum levels.[18]

The next step was to create chimeric and humanised forms of monoclonal antibodies, which would combine sequences from mouse and human sources and reduce the problems with immunogenicity. A number of these are now on the market.[18] By using phage-display technologies and transgenic animals, researchers have been able to develop fully human monoclonal antibodies. Nelson et al. expects fully human monoclonal antibodies to dominate R&D because of the lower levels of immunogenicity; over the past 10 years, 45 % of the candidates in clinical development are fully human.[18]

Fully human monoclonal antibodies tend to be less immunogenic, but the causes of immunogenicity are not fully understood. Immunogenic responses vary between antibodies and diseases and are affected by

the administration of other drugs.[18] For example, the fully human antibodies panitumumab and adalimumab showed immunogenic responses in 1 % and 5 % of patients, respectively, but less than 1 % of patients receiving rituximab, a chimeric monoclonal antibody, showed immunogenicity.[18,24,25]

Monoclonal antibodies are by nature specific, and while they can be very effective in patients who express the specific target, they are ineffective in patients not carrying the relevant biomarker. For example, only around 25 % of breast cancers are HER2 positive, and patients who are HER2 negative will not respond to trastuzumab.[26] Finding patients with the right biomarkers requires the use of companion diagnostics.

Patients can also develop resistance to monoclonal antibody therapeutics. Trastuzumab is only effective in 30 % of patients who are HER2 positive.[26]

Biologicals, including monoclonal antibodies, tend to be expensive because of the high costs of development, which can restrict their use to specific groups of patients. The requirement for companion diagnostics further increases the costs. Generic forms of some biologicals, known as biogenerics or biosimilars, are in development, but this is a long and slow process.

New Approaches

Although monoclonal antibodies are highly effective – even curative – for some groups of patients, and have lower rates of side effects, all is not lost for cytotoxics.They have been around for a long time and there is an abundance of data available on their modes of action. Based on these data, academics and industry scientists have developed newer cytotoxics that are more effective and have fewer side effects because they target specific pathways or can be used at lower doses. Cytotoxic agents will also have ongoing use in patients who do not express the right biomarkers for targeted therapies, or as combination therapy with targeted therapeutics. This next section of the article is not exhaustive, but provides examples of recent approaches to different cytotoxics.

Newer Cytotoxics

To address the toxicity and resistance issues associated with platinum-based compounds, some researchers are focusing on organometallic compounds. In a 2011 review by Gasser et al.,[7] metallocenes, organometallic complexes, organometallics, metal carbene complexes and metal carbonyl complexes were analysed. These compounds seem to be stable and are well characterised. They have a range of modes of action, including protein interactions – for example with hormonal receptors, cyclooxygenases and kinases – and novel, metal-specific modes of action. While there do not appear to be any organometallic compounds in clinical trials for cancer, the ferrocene derivative ferrocerone is approved in Russia for anaemia, and ferroquine has undergone phase II trials for malaria.[7]

Some tumours develop resistance to taxanes. To address this issue, research is under way into taxane derivatives.[27] Larotaxel is an example of a taxane derivative and, while it has not been approved for launch, it gives an indication of the directions for development. Larotaxel is a semi-synthetic taxoid prepared from 10-deacetyl baccatin III, a compound extracted from yew trees. In preclinical studies, larotaxel showed activity against multidrug-resistant tumours. Larotaxel showed activity alone and in combination with trastuzumab in patients with metastatic breast cancer, including those with taxane-resistant disease.[27] It was studied in phase III trials in advanced prostate cancer and showed activity but no survival benefit.[28] As part of R&D restructuring, Sanofi-aventis terminated the development of larotaxel in February 2010.[29]

Table 2: Monoclonal Antibodies Combined with Cytotoxic Agents (Approved or in Clinical Trials)

Monoclonal Antibody	Indication	Cytotoxic Agent
Bevacizumab	Metastatic colorectal cancer	Fluoropyrimidine-based chemotherapy
	Metastatic breast cancer	Paclitaxel or docetaxel
	Metastatic or recurrent non-small cell lung cancer	Platinum-based chemotherapy
Cetuximab	Squamous cell cancer of the head and neck	Platinum-based chemotherapy
Trastuzumab	Metastatic breast cancer	Paclitaxel or docetaxel
		Aromatase inhibitors
		Anthracyclines
		Vinorelbine or vinflunine
		Doxorubicin cyclophosphamide and paclitaxel
	Metastatic gastric cancer	Capecitabine or fluorouracil and cisplatin
Rituximab	Non-Hodgkin's lymphoma	CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)

Sources: BNF, 2011;[12] Wilkins and Begent, 2002;[22] Olver, 2008;[33] Vose, et al., 2005.[34]

Vinflunine is a synthetic fluorinated vinca alkaloid originally developed by Pierre Fabre. It has shown greater efficacy than vinorelbine in preclinical trials,[30] and was effective in patients with advanced transitional cell carcinoma of the urothelium in phase III trials. The side effects were non-cumulative and medically manageable.[31]

Vinflunine is approved for marketing in Europe and is in phase III trials in the US. However, the National Institute for Health and Clinical Excellence in England and Wales and the Scottish Medicines Consortium in Scotland do not recommend vinflunine for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.[32]

Combination Regimens

A number of monoclonal antibodies have been licensed or are being studied for use in combination with cytotoxic agents.[12] Examples are presented in *Table 2*.[12,22,33,34] The advantage of combination regimens is that responses can improve, resistance is less likely to develop, and doses of cytotoxic agents may be decreased, therefore reducing side effects. Combination therapies may be effective in patients who have stopped responding to single agents.

Targeting Cytotoxics to Tumours

When cytotoxic agents are administered systemically, as little as 5–10 % of the active agent may reach the tumour site, and this can lead to disease relapse, drug resistance[35] and unwanted side effects. Complexing single cytotoxic agents or combinations of cytotoxic

agents with molecules or technologies that target the therapeutics to the tumour could improve responses, slow the development of resistance, and reduce side effects because of reduced systemic exposure. This strategy will also reduce the dose required, which could cut the costs of expensive agents. This could include approaches that target a specific marker or are physically localised to the tumour.

Using a molecule that binds specifically to tumour cells is an effective way of targeting cytotoxic drugs to tumours. Abraxis BioScience (now Celgene Corporation) developed a solvent-free nanoparticle formulation of paclitaxel (130-nanometre albumin-bound paclitaxel or nab-paclitaxel). The albumin promotes internalisation of the nanoparticles and binds to SPARC (secreted protein, acidic and rich in cysteine), which is overexpressed on certain tumour cells.[14]

A meta-analysis of clinical trials showed that the albumin formulation improved the safety and side-effect profile, allowing higher doses and shorter infusion times without premedication. Patients receiving nab-paclitaxel had an improved tumour response rate and progression-free intervals, but no survival benefit except in second-line or later treatment.[14] This has been approved for the treatment of metastatic breast cancer as Abraxane® and is in phase III trials for advanced lung cancer, malignant melanoma and advanced pancreatic cancer, and phase II trials for bladder and ovarian cancer. Celgene is also developing nab formulations of docetaxel (ABI-008 – phase II) for hormone-refractory prostate cancer, and of rapamycin (ABI-009 – phase I), 17AAG (ABI-010 – preclinical) and thiocolchicine dimer (ABI-011 – preclinical) for solid tumours.[36]

Kolishetti et al. have created a self-assembled polylactide derivative nanoparticle that co-delivers cisplatin and docetaxel.[37] The nanoparticle incorporates the A10 aptamer, which binds to the prostate-specific membrane antigen (PSMA) on prostate cancer cells, and this was endocytosed by PSMA-expressing LNCaP prostate cancer cells, with higher toxicity than single-drug or non-targeted nanoparticles.[37]

Using the physiology of organs or tumours can physically localise cytotoxics to tumours. Cancer tissues tend to have 'leaky' blood vessels because of the rapid neo-vascularisation needed for rapidly growing tumours and the lack of an effective lymphatic system.[38] This leads to enhanced permeation and retention of particles such as nanoparticles and liposomes, allowing passive tumour targeting of cytotoxic therapeutics.

Biocompatibles UK has developed a sulfonate-modified polyvinyl alcohol hydrogel matrix called DC Bead® that can be loaded with cytotoxic agents. The beads are used in transarterial chemoembolisation, which blocks the peripheral blood vessels feeding the tumour and delivers cytotoxic drugs locally. They can also be administered intraperitoneally or intratumourally, and have been studied using doxorubicin, mitoxantrone, irinotecan and topotecan.[39]

Something as simple as a magnetic field can physically localise cytotoxics to tumours. The use of magnetic particles allows drugs to be physically localised to the area of a tumour by using an external magnetic source. Wang et al. looked at the use of biocompatible and biodegradable superparamagnetic iron oxide nanoparticles as a sustained release and localisable delivery system for the cytotoxic drug daunorubicin.[40] The particles were made up of an iron oxide core coated with oleic acid and daunorubicin, with a stabilising coat of Pluronic® F-127, a non-ionic, surfactant polyol. Preclinical studies showed that the particles could be loaded with up to 10 % drug, and that 20 % of this was released over two days and 42 % over five days.

Erythrocytes (red blood cells) can carry proteins, peptides, nucleotide analogues and glucocorticoid analogues, and deliver them over days or weeks. Autologous red blood cells have the advantage of not inducing an allergic reaction. Researchers have looked at the feasibility of using erythrocytes as delivery vehicles. These would contain the cytotoxic pro-drug decitabine, with magnetic particles to localise the delivery and haemagglutinin viral spike fusion proteins to improve the fusion with target cells. *In vitro* studies have shown that erythrocytes are effective at incorporating the active agent, and that the haemagglutinin viral spike fusion proteins improve the uptake of the drug into the HeLa tumour cells compared with the drug alone, as shown by fluorescence studies. At 96 hours, 13 % of cells treated with the free drug showed apoptosis compared with 96 % treated with the loaded erythrocytes.[41]

Some molecules associate preferentially with cancer cells without specific targeting. A review by Moribe et al. looked at the use of ascorbyl n-alkyl fatty acid derivatives to create drug nanoparticles for cytotoxic agents.[42] Ascorbic acid derivatives have intrinsic anticancer activity and seem to enhance the activity of other agents. *In vitro* studies of paclitaxel liposomes incorporating ascorbyl-6-palmitate (ASC-P) showed that the liposomes associated preferentially with cancer cells rather than non-cancer cells. The addition of ASC-P also enhanced the cytotoxicity of paclitaxel. Another ascorbic acid derivative, L-ascorbic acid 6-stearate, in polymeric nanoparticles with transdehydrocrotonin, also showed preferential uptake and increased activity in tumour cells.[42]

Monoclonal antibodies and cytotoxics can combine to create a specifically targeted treatment, known as antibody–drug conjugates or armed antibodies. An example is trastuzumab emtansine (or trastuzumab-DM1), which combines the monoclonal antibody trastuzumab with the cytotoxic macrolide mertansine. In clinical trials, trastuzumab emtansine showed efficacy in advanced and metastatic breast cancer and was well tolerated.[27,43] Phase III trials are under way and the developer Genentech expects to submit trastuzumab emtansine for approval mid 2012 for advanced HER2-positive breast cancer, based on data from a revised clinical trial.[44] Ongoing comparative phase III trials are expected to be completed in August 2013 and July 2017.[43]

Other monoclonal antibody conjugates in phase III trials in 2011 include naptumomab estafenatox (Active Biotech Research), with staphylococcal enterotoxin A as the cytotoxic agent, and brentuximab vedotin (Seattle Genetics), with monomethyl auristatin E.[43]

Pro-drugs

Pro-drugs are administered in an inactive form and are preferentially activated at the tumour site. As an example of a widely available pro-drug, capecitabine is an oral precursor of 5-FU. It is preferentially converted into 5-FU in tumour cells, therefore reducing toxicity, and its oral administration allows treatment outside the clinical setting.[8]

Currently in a phase I/II trial at CellAct Pharma, CAP 7.1® is a small-molecule pro-drug of the cytotoxic agent etoposide, which is a topoisomerase II inhibitor. CAP 7.1 releases etoposide via specific carboxyesterases at the site of the tumour. This agent showed efficacy in drug-resistant tumours in animal models and induced responses in advanced and drug-resistant neuroblastoma in paediatric patients.[45] CAP 7.1 is well tolerated at significantly higher doses than etoposide and has also demonstrated efficacy in advanced stage cancers in adults.

Conclusion

In one form or another, cytotoxics have been used for over 70 years. Although they have a range of negative side effects, there is an abundance of data on them and they have improved or saved hundreds of thousands of lives. Researchers are working on a range of approaches to improve their toxicity profile, safety and efficacy. Cytotoxics should remain part of standard and new approaches to treat cancer, as part of delivery systems and pro-drugs, alone and in combination with biological and targeted therapeutic regimens. ■

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