PERSONAL PRACTICE

The use of immunosuppressive and cytotoxic drugs in non-malignant disease

P A Brogan, M J Dillon

Cytotoxic drugs prevent cell division or cause cell death. They act predominantly on rapidly dividing cells such as T lymphocytes, and are therefore immunosuppressive and anti-inflammatory. When cytotoxic drugs were initially used in the treatment of cancer, it became apparent that they had profound effects on the immune system. This “unwanted” side effect has subsequently been exploited for the treatment of non-malignant disease where autoimmune mechanisms are considered important in the pathogenesis.

More recently drugs such as cyclosporine, which act more specifically on the immune system via the inhibition of T lymphocyte function, are being used for the treatment of disease with immunologically mediated mechanisms.

Generally speaking cytotoxic drugs (CDs) have anticancer activity as well as immunosuppressive properties, whereas immunosuppressive drugs (ISDs) show a more specific immunosuppressive effect, although this distinction is partly arbitrary. For the purposes of this review we have adopted the classification described in the British National Formulary defining cyclosporine as an ISD; cyclophosphamide, vincristine, chlorambucil, and methotrexate as CDs; and azathioprine (and its active metabolite 6-mercaptopurine) and mycophenolate mofetil as “cytotoxic immunosuppressants”.

This review concentrates on the use of ISDs and CDs in the management of vasculitis and rheumatological disease, idiopathic nephrotic syndrome, and inflammatory bowel disease. For the majority of the disorders discussed treatment with ISDs and CDs will usually be initiated by clinicians with experience of the condition.

Reference to efficacy and safety of ISDs and CDs in children will be made. Specifically, the use of ISDs and CDs in organ transplantation will not be addressed.

Mechanism of action

CDs act primarily on rapidly dividing cells such as malignant cells, or those of the immune system, particularly T lymphocytes. Thus CDs have both anti-inflammatory and immunosuppressive effects. Azathioprine (and its metabolite 6-mercaptopurine) and mycophenolate mofetil inhibit biosynthesis of purines and act during the G₁ and S phases of the cell cycle of proliferating cells. Cyclophosphamide and chlorambucil are alkylating agents and cross link DNA during all phases of the cell cycle whether or not a cell is replicating. Methotrexate blocks dihydrofolate reductase and inhibits purine ring synthesis during the G₀ and S phases of the cell cycle. Vincristine is a vinca alkaloid and spindle poison which inhibits mitosis, causing metaphase arrest of dividing cells.

Cyclosporine is a calcineurin inhibitor which blocks the production of several cytokines including interleukin 2 (IL-2), IL-3, and IL-4, as well as interfering with the expression of the IL-2 receptor (CD25), thus preventing the activation of T cells. In contrast with CDs, this ISD has a more specific effect on the immune system, predominantly inhibiting T₁ lymphocytes.

Guidelines for the use and monitoring of cytotoxic and immunosuppressive drugs

ISDs and CDs undoubtedly play an important role in the treatment of many autoimmune diseases. Nonetheless these drugs themselves are associated with significant morbidity and even mortality. It is therefore of particular importance that the benefits and risks of ISDs and CDs are weighed when considering their use in the treatment of non-malignant disease.

Table 1 summarises general guidelines for the use of ISDs and CDs in non-malignant disease. The underlying disease can influence drug side effects in many ways and it is often difficult to attribute adverse events to disease, treatment, or a combination of both. Despite this, it has become apparent that individual drugs possess a specific toxicity profile.

Infection is a universal concern in patients receiving ISDs and CDs. Concomitant glucocorticoid therapy adds to this problem and

Table 1. Guidelines for the use of cytotoxic drugs in non-malignant disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>ISD/CD Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well established diagnosis</td>
<td>Allows</td>
</tr>
<tr>
<td>Severe, potentially life threatening disease</td>
<td>Allows</td>
</tr>
<tr>
<td>Inadequate response to less toxic therapy</td>
<td>Allows</td>
</tr>
<tr>
<td>No known infection or neoplasm</td>
<td>Allows</td>
</tr>
<tr>
<td>No pregnancy or possibility thereof</td>
<td>Allows</td>
</tr>
<tr>
<td>Informed consent obtained</td>
<td>Allows</td>
</tr>
<tr>
<td>Availability of adequate facilities to monitor and treat complications</td>
<td>Allows</td>
</tr>
</tbody>
</table>

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Table 2  Doses, side effects, and clinical monitoring of ISDs and CDs for the treatment of non-malignant disease*  

<table>
<thead>
<tr>
<th></th>
<th>Cyclophosphamide</th>
<th>Azathioprine</th>
<th>Chlorambucil</th>
<th>Methotrexate</th>
<th>Cyclophosphamide</th>
<th>Mycophenolate</th>
<th>Vincristine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dose</td>
<td>2–3 mg/kg OD PO 2–3 months; 0.5–1.0 g/m² IV monthly with MESNA to prevent cystitis</td>
<td>0.5–2.5 mg/kg OD PO for 1 year or more</td>
<td>0.1–0.2 mg/kg/day for 3 months</td>
<td>10–15 mg/m²/wk (single dose) PO</td>
<td>3–5 mg/kg/day PO (in 2 divided doses)</td>
<td>0.25–2 g/day (2 divided doses)</td>
<td>1.5 mg/m²/wk IV (single dose) for 8 weeks (limited data for efficacy in FSGS)</td>
</tr>
<tr>
<td>Serious side effects</td>
<td>Leucopenia; haemorrhagic cystitis; reversible alopecia; infertility; leukaemia, lymphoma, transition cell carcinoma of bladder</td>
<td>GI toxicity; hepatotoxicity; rash; leucopenia; teratogenicity; no increase in malignancy in adults with RA; no conclusive data for cancer risk in children</td>
<td>Marrow suppression; rash; toxic epidermal necrolysis; Stevens-Johnson syndrome; late risk of leukaemia?</td>
<td>Bone marrow suppression and interstitial pneumonitis (decreased risk with folic acid); reversible elevation of transaminases; hepatic fibrosis</td>
<td>Renal impairment; hypertension; hepatotoxicity; tremor; gingival hyperplasia; hypertrichosis; lymphoma</td>
<td>Bone marrow suppression; severe diarrhoea; pulmonary fibrosis</td>
<td>Reversible peripheral and autonomic neuropathy; SIADH; severe local irritation if extravasation; alopecia; constipation; myelosuppression rarely encountered</td>
</tr>
<tr>
<td>Cumulative toxic dose</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td>Clinical monitoring</td>
<td>Weekly FBC for duration of therapy (usually 2–3 months)*</td>
<td>Not described</td>
<td>&gt;18 mg/kg causes azosperma; &lt;10 mg/kg does not</td>
<td>Weekly clinical review and FBC for duration of therapy*</td>
<td>Baseline CXR, FBC and LFTs</td>
<td>Baseline CXR, FBC and LFTs</td>
<td>Weekly FBC for 2 months, then fortnightly for 2 months, then monthly</td>
</tr>
<tr>
<td></td>
<td>Baseline and monthly renal function</td>
<td>Baseline and monthly renal and liver function for 2 months, then 3 monthly</td>
<td>Baseline and monthly renal function</td>
<td>Baseline and monthly renal and liver function</td>
<td>Baseline and monthly renal function</td>
<td>Baseline and monthly renal function</td>
<td>Baseline and monthly FBC</td>
</tr>
<tr>
<td></td>
<td>Temporarily discontinue if leucopenia &lt;1.5 × 10⁹/l, platelets &lt;100 × 10⁹/l, or haematuria</td>
<td>Temporarily discontinue if leucopenia &lt;1.5 × 10⁹/l, platelets &lt;100 × 10⁹/l</td>
<td>Reduce or discontinue if hepatic enzymes &gt;3× upper limit of normal</td>
<td>Maintain 12 hour trough level at 50–100 mg/m²</td>
<td>Baseline and 3 monthly GFR</td>
<td>Discontinue if increasing neurotoxicity, especially motor weakness</td>
<td></td>
</tr>
</tbody>
</table>

*Personal practice.

should be administered as an alternate day regimen wherever possible. A detailed account of the plethora of opportunistic infections that can occur is beyond the scope of this article, however infection with cytomegalovirus, *Pneumocystis carinii*, and varicella zoster remain ever present concerns. Of particular concern regarding the use of ISDs and CDs in children is the long term cancer risk, although this risk has not been quantified in children. There is generally a lack of data regarding cumulative dose toxicity for the various agents mentioned above, but this is an important factor to bear in mind and should be discussed with parents and child before the onset of therapy. Other potential medium and long term side effects such as teratogenicity and infertility are also important considerations.  

Table 2 summarises the most important side effects and cumulative toxic doses (where known) of the common ISDs and CDs used in the treatment of autoimmune disease, and other diseases thought to be mediated by immunological processes, with guidelines for appropriate monitoring of individual drugs.  

**Immunisation**

It is our practice to advise against immunisation with all live vaccines (including varicella zoster) in children undergoing treatment with CDs and ISDs. Furthermore, there is potential for flaring of certain diseases (such as the vasculitides) following immunisation with non-live vaccines such as the recently introduced *Neisseria meningitidis* type C vaccine (personal observation). Thus the decision to immunise is influenced by the type of vaccine, the disease, and the disease treatment. Vaccination therefore needs to be considered carefully on an individual basis, and taking into account these specific aspects.  

**Vasculitis**

Vasculitis is a feature of many different diseases and syndromes in childhood, and may be the predominant manifestation of certain conditions, but in others may reflect one aspect of a more widespread connective tissue disorder.  

Classification of the various vasculitic disorders has proved difficult, and not entirely satisfactory. Moreover, the lack of a single pathognomonic test for the diagnosis of vasculitis, and also for the assessment of disease activity, makes prospective studies of vasculitis and its treatment even more difficult. Thus, data based on prospective double blind randomised controlled trials regarding the use of ISDs and CDs in the management of this complex group of disorders in the paediatric population is lacking, and many studies are retrospective and employ historical controls. Undoubtedly, however, the use of ISDs and CDs plays a crucial role in the management of these patients.  

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POLYARTERITIS—POLYARTERITIS NODOSA AND MICROSCOPIC POLYANGIOPATHY

Polyarteritis nodosa is a necrotising vasculitis associated with aneurysmal nodules along the walls of medium sized muscular arteries. Although there is an overlap with smaller vessel disease, it is distinct from microscopic polyangiopathy, and occurs more commonly in childhood than this latter disorder. The main clinical features are malaise, fever, skin rash, abdominal pain, and arthralgy. Other features include testicular pain, myalgia, hypertension, neuropathy, renal failure, organic psychosis, and myocardial ischaemia. Visceral angiography plays a key role in the diagnosis.

Microscopic polyarteritis may be defined as small vessel vasculitis with focal segmental glomerulonephritis, but without granulomatosus disease of the respiratory tract. Clinically, it can be difficult to distinguish from Wegener’s granulomatosis, and often presents with rapidly progressive glomerulonephritis.

The aims of treatment of systemic vasculitides are to induce remission and improve survival; to limit disease related morbidity and maintain remission; and to limit the consequences of the toxicity of treatment regimens. Treatment for both microscopic and microscopic polyarteritis consists of steroids, antiplatelet agents, and an additional cytotoxic agent, usually cyclophosphamide. Cyclophosphamide is usually administered orally for two to three months at 2 mg/kg/day to induce remission.

Pulsed intravenous cyclophosphamide may have advantages over the oral route in reducing the total cumulative dose and hence side effects, but it may not be as effective as the daily oral regimen in aggressive disease for the prevention of relapses. Maintenance therapy is usually with oral azathioprine at a dose of 2 mg/kg/day, with low dose alternate day prednisolone (0.2–0.5 mg/kg), and antiplatelet agents. If remission with this regimen is not maintained, then cyclosporine or mycophenolate mofetil may prove useful, although the published evidence for the use of these agents in this context is lacking.

Currently, the mortality for polyarteritis nodosa at Great Ormond Street Hospital, London is about 10%, which compares favourably with many adult series.

WEGENER’S GRANULOMATOSIS

Wegener’s granulomatosis is a necrotising granulomatous vasculitis of the upper and lower respiratory tract, associated with glomerulonephritis and variable small vessel vasculitis. Treatment is similar to polyarteritis and includes steroids, cyclophosphamide, antiplatelet agents, and prophylactic antibiotics such as cotrimoxazole, with plasma exchange if necessary to treat relapses. The mortality for Wegener’s granulomatosis at Great Ormond Street Hospital is currently around 15%.

MISCELLANEOUS VASCULITIS

Takayasu disease is a giant cell arteritis causing stenosis and aneurysmal dilatation of large arteries, such as the aorta and its major branches. Worldwide, it is the third commonest vasculitis of childhood, and may be related to infection with tuberculosis. Clinical features include fever, anorexia, weight loss, arthritis, and later the development of hypertension, heart failure, and pulse deficits. Diagnosis involves Doppler ultrasonography, magnetic resonance imaging, and conventional angiography. Therapeutic regimens in the acute phase of the disease include steroids, cyclophosphamide, and methotrexate. More recently, there have been case reports of the successful treatment of Takayasu disease with mycophenolate mofetil.

Behçet’s disease consists of the triad of aphthous stomatitis, genital ulceration, and iritis; a vasculitic component to the illness is an important feature. The disorder is often difficult to treat, and some patients do not respond with steroids alone, especially if there is central nervous system or ocular involvement. Colchicine and levamisole may also play a role.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, multisystemic disease with a multifactorial aetiology. Before modern treatment techniques appeared, the majority of children died either from lupus involving multiple organs, including the kidneys, or from infections. The advent of steroids, CDs, and ISDs in the management of SLE has led to a five year survival of 95% in most centres. However, of those who do succumb to the disease, infection as a result of immune suppression plays an important role. Other causes of death include chronic renal failure, myocardial infarction, or pulmonary disease.

The deposition of circulating autoantibodies or autoantibody containing complexes along the endothelium of glomerular capillaries is believed to initiate complement mediated inflammation and ultimately end organ damage. Intravenous cyclophosphamide in SLE has been best studied in lupus nephritis, for which controlled trials have shown clear evidence for the benefit of pulsed intravenous cyclophosphamide over steroids alone in reducing clinical and serological activity of lupus, histological damage, and end stage renal failure. Before the routine use of cyclophosphamide, the prognosis for children with continuing active renal disease following corticosteroid therapy alone was poor, although lupus nephritis had been treated moderately successfully in the past with corticosteroids and azathioprine.

Cyclophosphamide can be administered intravenously in 500–1000 mg/m² monthly pulses (based on the NIH protocol) for diffuse proliferative glomerulonephritis (DPGN, WHO class IV lupus nephritis). The optimal
duration of treatment with intravenous cyclophosphamide has not been determined for a child with DPGN, but treatment for six months (seven pulses), followed by three monthly pulses would be typical, followed by maintenance therapy with prednisolone (0.3–0.5 mg/kg/day, or alternate day), and azathioprine (2–2.5 mg/kg/day). Continuing pulse cyclophosphamide for at least one year after achievement of stable remission is associated with decreased probability of subsequent nephritic flares in adults, although this latter approach may not be suitable for children, in whom longer term cancer risk is an issue.

Oral cyclophosphamide at 2 mg/kg/day for two to three months is an alternative regimen to induce remission of lupus nephritis. As with the intravenous regimen, this can be followed by maintenance therapy with oral prednisolone plus azathioprine.

Although it is clear that such regimens have improved efficacy over steroids alone in the treatment of lupus nephritis, no immunosuppressive agent has been shown to be statistically more effective than another for either total mortality or end stage renal failure. It has been suggested, however, that intravenous cyclophosphamide has a better therapeutic index than oral cyclophosphamide.

A critical point is the termination or dose reduction of CDs and ISDs when side effects such as marrow suppression exceed the benefits, for example if the kidneys are failing despite treatment, or if on renal biopsy there is little evidence of disease activity. It is worth emphasising in this context that lupus nephritis is very rare in renal transplants.

**Juvenile dermatomyositis**

Vasculitis is a major component of juvenile dermatomyositis (JDM), and can pose a major threat to life. The vasculitis affects striated muscle, skin, subcutaneous tissue, and gastrointestinal tract. Gastrointestinal perforation, bleeding, and acute pancreatitis can all result from mesenteric vasculitis. Treatment of severe disease typically includes steroid, oral or intravenous cyclophosphamide plus, in life threatening situations, plasma exchange. Methotrexate and cyclosporine have also been shown to be effective in this disease, and indeed many would initially treat JDM with a combination of prednisolone and cyclosporine, reserving more aggressive treatment modalities for those in whom severe features emerge.

**Juvenile idiopathic arthritis**

It is generally agreed that chronic arthritis in childhood is a heterogeneous group of disorders, the majority of which are different from seropositive rheumatoid arthritis in adults. Previously termed JCA (juvenile chronic arthritis), juvenile idiopathic arthritis (JIA) is divided into three broad clinical groups: systemic JIA (Still’s disease), polyarticular JIA, and pauciarticular JIA. CDs and ISDs used to treat JIA include methotrexate (MTX), azathioprine, cyclosporine, cyclophosphamide, and for uveitis and renal amyloidosis chlorambucil.

With the exception of methotrexate, experience with cytotoxic drugs in JIA is largely anecdotal or uncontrolled. Low dose methotrexate is administered at a dose of 10–15 mg/m² orally once a week, with folic acid to reduce marrow toxicity. MTX is now considered a second line agent, and appears to confer greatest benefit in those with extended oligoarticular disease.

**Idiopathic nephrotic syndrome**

The nephrotic syndrome (NS) is characterised by heavy proteinuria, hypoalbuminaemia, and oedema. Steroid sensitive NS affecting the majority of children is a relatively mild form of the disease, virtually without impairment of glomerular filtration rate. Steroid resistant NS and refractory NS such as that seen in focal segmental glomerulosclerosis have an unfavourable prognosis, tending often towards chronic renal failure. There is a growing enthusiasm for more aggressive treatment of these latter clinical entities with CDs and ISDs in an attempt to preserve renal function.

Various CDs and ISDs have been used for the treatment of steroid resistant and steroid dependent NS (the latter if steroid toxicity becomes unacceptable), with varied results. Oral cyclophosphamide (2–3 mg/kg/day for two to three months), chlorambucil (0.15–0.2 mg/kg/day for two to three months), and cyclosporine (5–6 mg/kg/day) are the most commonly used. It has been suggested that intravenous pulsed cyclophosphamide may be more effective than the oral route, with more sustained remissions, fewer side effects, and at a lower cumulative dose.

However, in a prospective randomised controlled trial, oral cyclophosphamide failed to confer any benefit over alternate day prednisolone in 60 children with biopsy proven focal segmental glomerulosclerosis complicated by steroid resistant NS. One quarter of the children in each group had complete resolution of proteinuria. Indeed, treatment failure as defined by a rise in serum creatinine of 30% or more, was higher in the cyclophosphamide treated group, although this difference did not reach statistical significance.

A prospective randomised controlled trial of cyclosporine therapy (5–6 mg/kg/day) for one year, versus supportive therapy alone for steroid resistant INS in 45 patients (17 children), showed that cyclosporine induced remission in 65% of patients compared with 16% in the supportive therapy group. Relapse rates appear to be high, however, when the drug is discontinued; thus cyclosporine may have to be continued for long periods.

There are limited data supporting the use of vincristine in the treatment of focal segmental glomerulosclerosis, although for some patients a clear benefit has been shown.

**Inflammatory bowel disease**

The evidence for the current approach to the use of CDs and ISDs in inflammatory bowel disease (IBD) is based on many observational studies and randomised controlled trials. A recent meta-analysis of randomised, placebo
controlled trials of azathioprine and its active metabolite 6-mercaptopurine for the induction of remission in 177 adults with Crohn's disease revealed a response rate of 56% in the treatment group. Interestingly, the response rate to placebo was 32%, emphasising the importance of controlled trials to evaluate IBD. The same meta-analysis also showed the ability of azathioprine to maintain remission, with an overall response rate of 67%, although therapy needed to be maintained for longer than 17 weeks before substantial efficacy was observed.

Azathioprine has also been shown to be useful as a steroid sparing agent in glucocorticoid dependent ulcerative colitis, and for maintenance of remission.

Other disorders where ISDs and CDs are effective for the treatment of inflammatory bowel disease include methotrexate, cyclosporine, and mycophenolate mofetil.

Other disorders where ISDs and CDs are effective therapeutically include mixed connective tissue disease (cyclophosphamide, methotrexate, sleroderma (azathioprine, chlorambucil, methotrexate, cyclosporine), chronic active hepatitis (cyclosporine, tacrolimus), sarcoidosis (methotrexate, cyclophosphamide), as well as other glomerulonephritides such as membranous nephropathy (cyclophosphamide, chlorambucil, and cyclosporine), membranoproliferative glomerulonephritis (cyclophosphamide), although use controversial), and Goodpasture disease (cyclophosphamide).

Conclusion

CDs and ISDs are an important part of the therapeutic approach to many non-malignant autoimmune disease disorders. They are not a panacea, however, because they do not prevent the relapse of disease in many instances, and have significant side effects which in themselves are associated with substantial morbidity and mortality. Improved understanding of the immune system in health and disease should reveal new therapeutic approaches, perhaps with less toxicity.


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