Clinical aspects of a phase I trial of 5,6-dimethylxanthenone-4-acetic acid (DMXAA), a novel antivascular agent

MB Jameson, PI Thompson, BC Baguley, BD Evans, VJ Harvey, DJ Porter, MR McCrystal, M Small, K Bellenger, L Gumbrell, GW Halbert and P Kestell on behalf of the Phase I/II Trials Committee of Cancer Research UK

The antitumour action of 5,6-dimethylxanthenone-4-acetic acid (DMXAA) is mediated through tumour-selective antivascular effects and cytokine induction. This clinical phase I trial was conducted to examine its toxicity, maximum tolerated dose, pharmacokinetics (PK) and pharmacodynamics (PD). A secondary objective was to assess its antitumour efficacy. DMXAA was administered every 3 weeks as a 20-min i.v. infusion. Dose escalation initially followed a modified Fibonacci schema but was also guided by PK and toxicity. A total of 63 patients received 161 courses of DMXAA over 19 dose levels ranging from 6 to 4900 mg m

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Targeting tumour vasculature as a treatment for cancer is the subject of much research, with most effort currently directed at angiogenesis inhibitors. Yet therapies that interrupt existing tumour vasculature and result in haemorrhagic necrosis of tumours have been investigated for over a century and were mostly associated with bacterial infections or their toxins (Chaplin and Dougherty, 1999). William Coley, who pursued the method avidly from 1891 (Council on Pharmacy and Chemistry, 1934), achieved significant cure rates, especially in sarcoma and lymphoma, using various bacterial toxins both for advanced disease and as adjuvant therapy (Coley-Nauts et al., 1953). Coley’s toxins were abandoned in favour of radiotherapy, but more recent clinical studies with bacterial endotoxins have shown modest antitumour activity, although systemic toxicity remains dose-limiting (Otto et al., 1996; DeVore et al., 1997).

In 1947, investigators at the National Cancer Institute observed that a toxin from the bacterium Serratia marcescens acutely and irreversibly reduced blood flow to sarcomas in mice, while blood flow to muscle recovered within 18 h (Algire et al., 1947). The induction of tumour necrosis factor (TNF) by bacterial toxins was later shown to be the cause of haemorrhagic necrosis in tumours (Carswell et al., 1975; Old, 1985). Clinical trials of recombinant human TNF were unable to deliver therapeutic doses systemically because of toxicity (Spriggs and Yates, 1992), but TNF is highly effective in conjunction with chemotherapy in isolated limb perfusion for melanoma and sarcoma, where it has been shown to have selective tumour vascular effects (Lejeune et al., 1998; Ruegg et al., 1998; Eggermont and ten Hagen, 2001).

Nonbacterial, tumour vascular-targeting agents could have advantages over bacterial products in terms of toxicity and pharmacology. One such agent, flavone acetic acid (FAA), showed remarkable anticancer activity in murine models (O’Dwyer et al., 1987) but its activity was minimal in clinical trials, although these were conducted when it was thought to be directly cytotoxic and its indirect mechanisms of antitumour action were poorly understood (Kerr and Kaye, 1989; Bibby, 1991). Further preclinical studies at the Auckland Cancer Society Research Centre (ACSRC) showed that FAA induced TNF production, acute tumour vascular collapse, haemorrhagic necrosis of tumours and enhanced activity of immune effector cells (Ching and Baguley, 1987; Smith et al., 1987; Finlay et al., 1988; Zwi et al., 1989, 1992) (Zwi et al., 1990 ID: 286). Few appropriate pharmacodynamic (PD) studies were performed in the clinical trials of FAA, so it is not known whether it has significant antivascular or immunological activity in humans. However, in vitro studies suggested a species difference in antitumour activity, because FAA induced TNF in murine, but not human, peripheral blood mononuclear cells (Ching et al., 1994; Philpott et al., 1997).
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5,6-Dimethylxanthenone-4-acetic acid (DMXAA), a new analogue of FAA developed in the ACSRC, showed greater activity and 12-fold higher dose-potency than FAA in murine tumour models (Rewcastle et al, 1991) and appeared to overcome the species difference in in vitro TNF production (Ching et al, 1994; Philipott et al, 1997). Dose-limiting toxicity in mice was consistent with hypotension, and was not strictly related to TNF production (Philipott et al, 1995). While DMXAA proceeded into clinical development because of this favourable profile, further studies in animal tumour models have demonstrated synergistic interactions between DMXAA with radiotherapy (Wilson et al, 1998), chemotherapy (particularly taxanes) (Pruijn et al, 1999; Horsman et al, 1999; Wilson and Baguley 2000; Siim et al, 2002), bioreducive cytotoxic drugs (Cliffe et al, 1994; Lash et al, 1998), radioimmunotherapy (Pedley et al, 1996), antibody-directed enzyme prodrug therapy (ADEPT) (Pedley et al, 1999), thalidomide (Cao et al, 1999) and immunotherapy (Kanwar et al, 2001).

Cancer Research UK selected DMXAA for two parallel phase I trials with different schedules, one in the UK using a weekly administration schedule (at Mt Vernon Hospital, Northwood, and Bradford Royal Infirmary, Bradford) and the other in Auckland, NZ, dosing every 3 weeks. The objectives of the NZ study were to determine the toxicity of DMXAA, its maximum tolerated dose (MTD), pharmacokinetics (PK), selected PD end points and, as a secondary objective, antitumour efficacy. A protocol amendment permitted evaluation of changes in tumour blood flow by dynamic magnetic resonance imaging (MRI) and the findings (including both UK and NZ trial patients) have recently been published (Galbraith et al, 2002). This report focuses on clinical aspects of the NZ trial; PD and PK aspects, due to their complexity, will be reported separately.

MATERIALS AND METHODS

Patients

Eligibility criteria included: patients ≥ 18 years with histologically or cytologically proven cancer refractory or not amenable to conventional therapy; WHO performance status of 0–2; life expectancy > 3 months; haemoglobin ≥ 9 g dl⁻¹; WBC ≥ 3 x 10⁹ l⁻¹; platelets ≥ 100 x 10⁹ l⁻¹; creatinine ≤ 130 μmol l⁻¹; bilirubin within normal limits, ALT and alkaline phosphatase < 2 x upper limit of normal unless due to liver and/or bone metastases; coagulation (international normalised ratio (INR) and activated partial thromboplastin time (APTT)) within normal limits; not pregnant or lactating (adequate contraception if capable of child-bearing); no anticancer therapy within 4 weeks (6 weeks for nitrosoureas and mitomycin C); no other serious medical conditions, uncontrolled infection or serious infection within 28 days; no glucocorticoid treatment in excess of physiological conditions, uncontrolled infection or serious infection within 28 days; no glucocorticoid treatment in excess of physiological conditions, uncontrolled infection or serious infection within 28 days; coagulation (international normalised ratio (INR) and APTT) were repeated 4 h after DMXAA infusion and 72 h after course 1 and 24 h after course 4. International chemistry and urinalysis. Complete blood count was repeated 24 h after course 1 (and on course 2 in one patient at each dose level) patients were hospitalised for 24 h to monitor toxicity and PK.

Patient assessments

Prior to treatment and weekly while on trial each patient had a history taken, clinical examination and blood tests including complete blood count (CBC) and differential, INR, APTT, chemistry and urinalysis. Complete blood count was repeated 24 and 72 h after course 1 and 24 h after course 4. International normalised ratio and APTT were repeated 4 h after DMXAA infusion on courses 1 and 4. Blood pressure and heart rate were monitored from 30 min before each infusion to 6 h afterwards. On course 1 (and on course 2 in one patient at each dose level) patients were hospitalised for 24 h to monitor toxicity and PK. Later in the trial, 24-h urine collections were made immediately prior to and after DMXAA administration, in order to evaluate changes in creatinine clearance. The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) Expanded Common Toxicity Criteria (CTC) was used to assess adverse events.

An electrocardiograph (ECG) was performed prior to trial entry. When transient prolongation of the cardiac corrected QT interval (QTc) was noticed in a patient after treatment with DMXAA at 2000 mg m⁻², subsequent patients had serial ECGs (in two patients) or ambulatory digital Holter ECG monitoring (in 12 patients) to evaluate acute changes in the QTc. The QTc was calculated using Bazett’s formula (QTc = QT/square root of

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Figure 1: Structure of DMXAA.
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Preceding R-R interval (Kligfield et al, 1996) and was measured in multiple ECG traces over the first 6–24 h after DMXAA administration.

Tumour response was assessed clinically each week, by plain radiographs every 3 weeks and by computed tomography (CT) or ultrasound scans every 6 weeks. A complete response was defined as the disappearance of all disease on two assessments at least 4 weeks apart. A partial response was defined as at least 50% decrease in the sum of the products of bidimensional measurements (or the sum of maximum diameters of lesions where bidimensional measurements were not feasible) of defined measurable lesions on two assessments at least 4 weeks apart, and no lesion should have progressed and no new lesions appeared. No change (static disease) was defined as less than 50% decrease and less than 25% increase in these measurements.

RESULTS

Patient characteristics

Table 1 summarises the gender, age, performance status, diagnosis and prior systemic therapy of patients enrolled onto the trial. A total of 161 courses were administered to 63 patients (60 individual patients, three of whom were re-enrolled at a higher dose level and evaluated as new patients). The median number of courses was 2 (range 1–8).

Dose escalation

Table 2 summarises the dose escalation schedule, number of courses administered and number of patients with DLT at each dose level. Where the investigators felt that specific toxicities were not of sufficient clinical concern, dose escalation continued without the dose level being expanded. One patient experienced DLT at the highest dose level and dropped one dose level for the second course, and is therefore represented twice. The dose was escalated from 6 to 4900 mg m⁻² over 19 dose levels. The first escalation (1.7-fold) followed the planned Fibonacci series, but the values of the area under the plasma concentration–time curve (AUC) at the first dose level were much lower (1/30th) than those predicted from murine data. Therefore, the dose was doubled for subsequent escalations. A rise in plasma nitrate (one of the PD end points measured) in a patient at 160 mg m⁻² suggested the possibility of having reached a PD threshold, and further escalations (1.2–1.5-fold) were guided by toxicity and PK from both the UK and NZ trials. Dose escalation was not restricted by non-haematological toxicities that technically met the protocol definition for DLT but were not considered of sufficient clinical significance (such as acute onset of tremor that resolved within one hour).

General toxicity

Toxicities of DMXAA were markedly different from those of many cytotoxic drugs, and many patients commented that it was easier to tolerate than chemotherapy. There was no significant drug-related neutropenia, thrombocytopenia or coagulopathy, and while anaemia and lymphocytopenia were common, they were judged unrelated to DMXAA in the majority of cases. Table 3 summarises selected drug-related non-haematological toxicities, which established the MTD at 3700 mg m⁻². At lower dose levels, this drug was generally well tolerated, with a minority of patients experiencing mild drug-related toxicity. Acute symptoms included venous discomfort with the infusion (alleviated by application of a warm pad), increased tumour pain several hours after the drug infusion and one patient briefly developed small urticarial lesions. Delayed toxicities included ‘flu-like’ symptoms (malaise, myalgia, fatigue, nausea, sweating) on days 2–4 of each course, but no mucositis or alopecia occurred. Additional acute toxicities were more prevalent with increasing dose above 1100 mg m⁻², with onset of symptoms during or shortly after the 20-min drug infusion. They were usually mild and invariably transient, generally resolving between a few minutes and 4 h later, and included nausea and/or vomiting (for

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### Table 1 Patient characteristics

| Characteristic                  | No. of patients |
|--------------------------------|-----------------|
| Total patients                 | 63              |
| Gender                         |                 |
| Male                           | 21              |
| Female                         | 42              |
| Age (years)                    |                 |
| Median                         | 55              |
| Range                          | 24–75           |
| WHO performance status         |                 |
| 0                              | 13              |
| 1                              | 22              |
| 2                              | 28              |
| Tumour primary site            |                 |
| Colon/rectum                   | 20              |
| Ovary                          | 11              |
| Melanoma                       | 6               |
| Lung                           | 5               |
| Breast                         | 3               |
| Cervix                         | 3               |
| Unknown primary                | 3               |
| Pancreas                       | 2               |
| Oesophagus                     | 2               |
| Kidney                         | 2               |
| Soft-tissue sarcoma            | 2               |
| Other                          | 4               |
| Previous treatment             |                 |
| Chemotherapy                   | 55              |
| Radiotherapy                   | 25              |
| Biotherapy/hormones            | 1               |
| None                           | 1               |

### Table 2 Dose escalation schedule

| DMXAA dose level (mg m⁻²) | No. of patients | No. of courses | Patients with DLT |
|---------------------------|-----------------|----------------|------------------|
| 6                         | 3               | 11             | 0                |
| 10.2                      | 3               | 9              | 0                |
| 20.4                      | 3               | 6              | 0                |
| 40.8                      | 3               | 6              | 0                |
| 81.6                      | 3               | 4              | 0                |
| 160                       | 3               | 6              | 0                |
| 240                       | 3               | 7              | 0                |
| 360                       | 3               | 6              | 0                |
| 500                       | 6               | 19             | 0                |
| 650                       | 3               | 6              | 0                |
| 850                       | 3               | 6              | 0                |
| 1100                      | 3               | 13             | 0                |
| 1375                      | 3               | 9              | 0                |
| 1650                      | 3               | 8              | 0                |
| 2000                      | 3               | 7              | 0                |
| 2600                      | 3               | 10             | 0                |
| 3100                      | 3               | 5              | 0                |
| 3700                      | 7               | 18             | 1                |
| 4900                      | 3               | 5              | 3                |

DLT = dose-limiting toxicity. *One patient treated at both dose levels.
Table 3  Nonhaematological toxicity (drug-relateda)

| Dose (mg m⁻²) | Nausea and/or vomiting | Venous pain | Malaise | Hyper- or hypotension | Flushing/sweating | Acute neuro symptoms | Dyspnoea |
|-------------|-------------------|-------------|--------|-------------------|-----------------|---------------------|---------|
|             | 1–2               | 3–4         | 1–2    | 3–4               | 1–2             | 3–4                 | 1–2    |
| 6           | 3                 | 1           |        |                   |                 |                     |        |
| 10.2        | 3                 | 1           | 2      |                   |                 |                     |        |
| 20.4        | 3                 | 1           | 1      |                   |                 |                     |        |
| 40.8        | 3                 | 1           |        |                   |                 |                     |        |
| 81.6        | 3                 | 1           |        |                   |                 |                     |        |
| 160         | 3                 | 1           |        |                   |                 |                     |        |
| 240         | 3                 | 1           |        |                   |                 |                     |        |
| 360         | 3                 | 1           |        |                   |                 |                     |        |
| 500         | 6                 | 2           | 1      | 2                 |                 |                     |        |
| 650         | 3                 | 2           | 1      |                   |                 |                     |        |
| 850         | 3                 | 2           | 1      |                   |                 |                     |        |
| 1100        | 3                 | 2           | 3      | 1                 |                 |                     |        |
| 1375        | 3                 | 3           | 1      | 2                 |                 |                     |        |
| 1650        | 3                 | 3           | 1      | 2                 |                 |                     |        |
| 2000        | 3                 | 2           | 2      | 1                 |                 |                     |        |
| 2600        | 3                 | 2           | 2      | 1                 |                 |                     |        |
| 3100        | 3                 | 2           | 2      | 1                 |                 |                     |        |
| 3700        | 7                 | 6           | 6      | 6                 |                 |                     |        |
| 4900        | 3                 | 3           | 3      | 3                 |                 |                     |        |

*aAlmost certainly, probably or possibly related to DMXAA. Neuro = neurological.

only a few minutes and not reliably prevented by ondansetron), sympathetic disturbance (sweating, warm flush, hypotension, bradycardia or tachycardia), altered taste and neurological disturbance (visual disturbance, tremor, feeling light-headed and restless). Patients at the higher dose levels also commonly experienced a brief urge to urinate and/or defecate. One patient (treated at 1650 mg m⁻²) had pre-existing impairment of bladder control and was incontinent of urine immediately following DMXAA administration. Creatinine clearance (measured by two sequential 24-h urine collections in 12 patients) did not change following DMXAA administration at doses ranging from 1375 to 4900 mg m⁻² (paired t-test, P = 0.63).

Neurological toxicity

At 4900 mg m⁻², acute neurological toxicity was considered dose limiting in all three patients, even though symptoms resolved completely within 2h. These included slurred speech (two patients), confusion and expressive dysphasia (one patient), moderate anxiety (one patient), severe visual disturbance (one patient), tremor (two patients) and urinary incontinence (one patient). Similar neurological toxicity was seen in one patient treated at 1650 mg m⁻² on her second course only, attributed to an interaction between DMXAA and isocarboxazid, a monoamine oxidase inhibitor. The features were consistent with the ‘serotonin syndrome’ (Sporer, 1995) and included difficulty concentrating, drowsiness, generalised tremor, occasional myoclonic jerks, hyper-reflexia, bradycardia and hypotension, all resolving within 6h.

Visual disturbance was first reported at 1375 mg m⁻² and symptoms became more prevalent and intense with increasing dose. Symptoms at lower dose levels included altered colour vision, blurring (without impairment of visual acuity) and mild photophobia. Colour vision testing revealed acute deterioration in colour discrimination, resolving within 4h. Dose-limiting transient visual disturbance at 4900 mg m⁻² included glintering of objects, harsh contrasts, jerky motion and strobe effects. Pattern and flash electroretinogram (ERG) showed an acute increase in latency and reduction in amplitude of certain retinal responses following DMXAA infusion with subsequent return to baseline over several hours, and a dose–response relationship was observed. A patient who received six courses at 3700 mg m⁻² showed subclinical deterioration of pre-infusion ERGs between courses 2 and 6.

Cardiorespiratory toxicity

Transient prolongation of the corrected cardiac QT interval was seen in all 13 patients evaluated at doses of 2000–4900 mg m⁻² (median prolongation 52 ms, range 38–100 ms). In six of nine patients with normal baseline QTc values, QTc became abnormally prolonged (>450 ms in males, >470 ms in females) after treatment with doses of DMXAA of ≥3100 mg m⁻² (Committee for Proprietary Medicinal Products, 1997). The maximal QTc prolongation occurred during or within 15 min of completion of the drug infusion with a return to baseline generally over 4–6 h (Figure 2). QTc was prolonged beyond 500 ms in four patients with baseline values of 430, 460, 461 and 501 ms and in the first three patients, this lasted for less than 1h. No clear dose–response relationship was observed and no ventricular tachyarrhythmia was seen.

Dyspnoea possibly related to DMXAA was documented in three patients treated at doses ≤1100 mg m⁻², but each patient had another more likely explanation. At higher doses, acute dyspnoea at rest occurred in four patients immediately following DMXAA infusion. In three of these patients (treated at 2600–3700 mg m⁻²), the dyspnoea after DMXAA was minimal, brief (5–25 min) and clinically insignificant. The fourth patient, with moderately severe chronic obstructive respiratory disease, became very breathless and anxious 15 min after her first course at 4900 mg m⁻². Clinically, she had basal pulmonary inspiratory crackles but no bronchospasm. Oxygen saturation was normal on breathing air and the symptoms resolved in about 75 min. On her second course, DMXAA was reduced to 3700 mg m⁻² (she is thus represented at two doses in Table 3) and she again developed dyspnoea, lasting for about an hour. She had basal inspiratory crackles and a third heart sound (consistent with left ventricular failure) and these signs resolved within 2h.
turbulence, as well as transient autonomic changes such as sweating, maintained for eight courses (Figure 3). No change was the best subsequently regressed again and overall tumour response was carboplatin. The response was unconfirmed because two small with bleomycin, etoposide and cisplatin chemotherapy, then carcinoma of cervix treated with DMXAA 1100 mg m$^{-2}$. The British Journal of Cancer (2003) 88 (Galbraith et al, 2002). The MTD was established as 3700 mg m$^{-2}$ Hours after DMXAA DMXAA trial, but no significant disturbance of INR and APTT was seen, nor was any significant thrombocytopenia observed. A number of other agents, including serotonin, some tubulin-binding agents and arsenic trioxide, selectively inhibit tumour blood flow (Stücker et al, 1992; Ching et al, 1999; Lew et al, 1999). Combretastatin A-4 phosphate (CA4P), a tubulin-binding agent, has antivascular activity at doses well below the MTD in both preclinical and early clinical studies (Rustin et al, 1999), comparable to those reported with DMXAA (Lash et al, 1998; Galbraith et al, 2002). However, the blood flow-modifying effect of CA4P is not entirely tumour-selective (Griggs et al, 2001), and it appears to be reversible except at high doses (Anderson et al, 1996; Murata et al, 2001). Some CA4P toxicities resembled those of DMXAA (including flushing, nausea, vomiting, tumour pain and QTc prolongation), but others (cardiac ischaemia and cerebellar ataxia) were notably different (Galbraith et al, 2001; Dowlati et al, 2002).

Some toxicities observed with DMXAA resemble the ‘serotonin syndrome’, attributed to high levels of serotonin in the central nervous system (CNS). This syndrome most commonly occurs when two drugs are taken, which can each increase CNS serotonin and includes alterations in cognition, behaviour, autonomic nervous system function and neuromuscular activity (Sporer, 1995). Supportive evidence comes from two other aspects of this trial: firstly, a patient took a monoamine oxidase inhibitor prior to treatment with DMXAA at 1650 mg m$^{-2}$ and developed clinical features of the serotonin syndrome; and secondly an acute increase in plasma prolactin levels seen in many patients treated with DMXAA at $\geq 2000$ mg m$^{-2}$ (unpublished results). This occurs following production of serotonin in the CNS (Van de Kar et al, 1996). If subsequent studies provide further evidence that DMXAA increases CNS serotonin release, it would be prudent to avoid administering DMXAA to patients who are receiving other drugs that increase CNS serotonin levels (Brown et al, 1996). The mechanism underlying the acute release of CNS serotonin is not known, but serotonin release in plasma has been observed in this study (Kestell et al, 2001), and is a feature of the antivascular activity of this drug in preclinical models (Baguley et al, 1997).

The visual toxicities of DMXAA are not a feature of the serotonin syndrome, but the blurring, colour disturbance and photophobia have similarities to those reported with sildenafil (Viagra®, Pfizer, New York, NY, USA) (Marmor and Kessler, 1999). The latter’s visual toxicities are thought to be due to inhibition of phosphodiesterase type 6 (PDE6), which exists exclusively in the retina and is responsible for modulating the transduction cascade of the photoreceptor response to light. Recent data have shown that DMXAA inhibited PDE6 in vitro at pharmacologically relevant concentrations (e.g. 50 μM) (personal communication, L Kelland, Antisoma plc). It is reassuring in this regard that no long-term retinal sequela of sildenafil administration is known, including data from retinal histologic

tremor, changes in blood pressure and heart rate. The results of the UK trial of DMXAA are published separately (Rustin et al, submitted to Br J Cancer), but there was a high degree of concordance with our results including toxicities, PK, PD and clinical activity (an unconfirmed partial response was also seen).

Clinical trials of FAA, which is structurally related to DMXAA, showed differences between the two drugs. While the clinical toxicities of DMXAA and FAA showed some similarities (warmth, flushing, sweating, fatigue, myalgia, nausea, vomiting and visual disturbance), the DLTs of FAA were remarkably different and included hypotension, diarrhoea, flushing, asthenia and fatigue (Kerr et al, 1987; Weiss et al, 1988; Kaye et al, 1990; Havlin et al, 1991; Olver et al, 1992). Prolongation of bleeding time was described (Rubin et al, 1987) and one patient presented with haemorrhage due to immune thrombocytopenia after five doses of FAA (Davis et al, 1988). Bleeding time was not measured in this DMXAA trial, but no significant disturbance of INR and APTT was seen, nor was any significant thrombocytopenia observed.

A total of 60 patients were evaluable for response. One partial response was seen in a patient with metastatic squamous carcinoma of cervix treated with DMXAA 1100 mg m$^{-2}$. Tumour size was calculated as the sum of the products of bidimensional measurements of three clinically measurable metastatic neck nodes.

**Therapeutic response**

A total of 60 patients were evaluable for response. One partial response was seen in a patient with metastatic squamous carcinoma of cervix treated at 1100 mg m$^{-2}$ and previously treated with bleomycin, etoposide and cisplatin chemotherapy, then carboplatin. The response was unconfirmed because two small neck nodes increased in size transiently after the third course then subsequently regressed again and overall tumour response was maintained for eight courses (Figure 3). No change was the best response in 22 patients (35%) at dose levels from 6 to 3700 mg m$^{-2}$ and the duration exceeded 12 weeks in five patients (8%).

**DISCUSSION**

This phase I trial of DMXAA has demonstrated clinical antitumour activity and reduction in tumour blood flow at well-tolerated doses (Galbraith et al, 2002). The MTD was established as 3700 mg m$^{-2}$, and higher doses produced unusual, transient toxicities including confusion, slurred speech, tremor, restlessness and visual disturbance, as well as transient autonomic changes such as sweating,
studies in dogs dosed with 65 times the maximum recommended human dose daily for 12 months (Wallis et al., 1998; Marmor and Kessler, 1999).

The significance of the observed QTc prolongation in these preliminary data is uncertain given its brevity, its possible relation to autonomic changes caused by the infusion and the population of patients potentially being treated with this agent. Moreover, the use of ad hoc heart rate correction formulae (such as Bazett’s) may bias the result (Aytemir et al., 1999). Therefore the QTc results in this trial must be regarded as indicative only. However, given the concern that QT interval prolongation may predispose to ventricular tachycardia (Committee for Proprietary Medicinal Products, 1997), it will be important to determine the dose-response relationship of QTc prolongation before deciding on the dose of DMXAA for phase II and combination studies.

In conclusion, DMXAA is well tolerated over a wide dose range and has clinical and biological features distinct from those of other antivascular drugs in clinical development. Further clinical trials with this agent are clearly warranted, particularly in combination with other treatment modalities where synergistic interactions are observed in animal tumour models.

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REFERENCES

Algie GH, Legallais FY, Park HD (1947) Vascular reactions of normal and malignant tissues in vitro. II. The vascular reaction of normal and neoplastic tissues of mice to a bacterial polysaccharide from Serratia marcescens (Bacillus prodigiosus) culture filtrates. J Natl Cancer Inst 8: 53 – 62

Anderson H, Jap J, Price P (2000) Measurement of tumour and normal tissue (NT) perfusion by positron emission tomography (PET) in the evaluation of antivascular therapy: results in the phase I study of combretastatin A4 phosphate (CA4P). Proc Annu Meet Am Soc Clin Oncol 19: 179

Aytemir K, Maarouf N, Gallagher MM, Yap YG, Waktare JE, Malik M (1999) Comparison of formulae for heart rate correction of QT interval in exercise electrocardiograms. Pacing Clin Electrophysiol 22: 1397 – 1401

Baguley BC, Zhuang L, Kestell P (1997) Increased plasma serotonin following treatment with flavone-8-acetic acid, 5,6-dimethoxyxanthenone-4-acetic acid, vinblastine, and colchicine–relation to vascular effects. Oncol Res 9: 55 – 60

Bibby MC (1991) Flavone acetic acid—an interesting novel therapeutic agent or just another disappointment. Br J Cancer 63: 3 – 5

Brown TM, Skip BP, Mareth TR (1996) Pathophysiology and management of the serotinin syndrome. Ann Pharmacother 30: 527 – 533

Cao Z, Joseph WR, Browne WL, Mountjoy KG, Palmer BD, Baguley BC, Chang LM (1999) Thalidomide increases both intra-tumoural tumour necrosis factor-alpha production and anti-tumour activity in response to 5,6-dimethoxyxanthenone-4-acetic acid. Br J Cancer 80: 716 – 723

Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B (1975) An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA 72: 3666 – 3670

Chaplin DJ, Dougherty GJ (1999) Tumour vasculature as a target for cancer therapy. Br J Cancer 80(Supp1): 57 – 64

Chang LM, Baguley BC (1987) Induction of natural killer cell activity by the antifolate compound flavone acetic acid (NSC 347 512). Eur J Cancer Clin Oncol 23: 1047 – 1050

Chang LM, Joseph WR, Crosier KE, Baguley BC (1994) Induction of tumour necrosis factor-alpha messenger RNA in human and murine cells by the flavone acetic acid analogue 5,6-dimethoxyxanthenone-4-acetic acid (NSC 640488). Cancer Res 54: 870 – 872

Chang LM, Wilson WR, Baguley BC (1999) Inhibition of tumour blood flow, In Methods in Molecular Medicine, Vol. 25, Drug Targeting, Francis, GE, Delgado, C (eds), Chapter 9, pp 1 – 26. Totowa, NJ: Humana Press Inc.

Cliffe S, Taylor ML, Rutland M, Baguley BC, Hill RP, Wilson WR (1994) Combining bioreductive drugs (SR 4233 or SN 23862) with the vasoactive antitumour compound flavone acetic acid (NSC 347 512). Int J Radiat Oncol Biol Phys 29: 373 – 377

Coley-Nauts H, Fowler GA, Bogatko FH (1953) A review of the influence of bacterial infection and bacterial products (Coley’s toxins) on malignant tumours in man. Acta Med Scand 145: 5 – 97

Committee for Proprietary Medicinal Products (1997) Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products, CPMP/896/96/1-6, URL: http://www.emea.eu.int/pdfs/human/swp/098696en.pdf

Council on Pharmacy and Chemistry (1934) Erysipelas and prodigious toxins (Coley). JAMA 103: 1067 – 1069

Davis HP, Newlands ES, Allain T, Hegde U (1988) Immune thrombocytopenia caused by flavone-8-acetic acid. Lancet 1(8582): 412

Devore RF, Helleqvist CG, Wakefield GB, Wamil BD, Thurman GB, Minton PA, Sundell HW, Yan HP, Carter CE, Wang YF, York GE, Zhang MH, Johnson DH (1997) Phase I study of the antineovascularization drug CM101. Clin Cancer Res 3: 365 – 372

Dowlati A, Robertson K, Cooney M, Petros WP, Stratford M, Jesterger J, Rafie N, Overmoyer B, Makkar V, Stambler B, Taylor A, Waas J, Levin JS, McCrae KR, Remick SC (2002) A Phase I pharmacokinetic and translational study of the novel vascular targeting agent combretastatin A-4 phosphate on a single-dose intravenous schedule in patients with advanced cancer. Cancer Res 62: 3408 – 3416

Eggermont AM, ten Hagen TL (2001) Isolated limb perfusion for extremity soft-tissue sarcomas, in-transit metastases, and other unresectable tumours: credits, debits, and future perspectives. Curr Oncol Rep 3: 359 – 367

Finlay GJ, Smith GP, Fray LM, Baguley BC (1988) Effect of flavone acetic acid on Lewis lung carcinoma: evidence for an indirect effect. J Natl Cancer Inst 80: 241 – 245

Galbraith SM, Lodge MA, Taylor NJ, Maxwell R, Tozer GM, Prise V, Wilson I, Sena L, Robbins A, Padhani A, Rustin G (2001) Combretastatin A4 phosphate (CA4P) reduces tumor blood flow in animals and man, demonstrated by MRI. Proc Annu Meet Am Soc Clin Oncol 20: 278a

Galbraith SM, Rustin GJ, Lodge MA, Taylor NJ, Stirling JJ, Jameson M, Thompson P, Hough D, Gumbrell L, Padhani AR (2002) Effects of 5,6-dimethoxyxanthenone-4-acetic acid on human tumor microcirculation assessed by dynamic contrast-enhanced magnetic resonance imaging. J Clin Oncol 20: 3826 – 3840

Griggs J, Hesketh R, Smith GA, Brindle KM, Metcalfe JC, Thomas GA, Williams ED (2001) Combretastatin-A4 disrupts neovascular development in non-neoplastic tissue. Br J Cancer 84: 832 – 835

Havlín KA, Kuhn JG, Craig JB, Boldt DH, Weiss GR, Koeller J, Harman G, Schwartz R, Clark GN, Von Hoff DD (1991) Phase I clinical and pharmacokinetic trial of flavone acetic acid. J Natl Cancer Inst 83: 124 – 128

Horsman MR, Murata R, Overgaard J (1999) Improving conventional cancer therapy by targeting tumour vasculature. Br J Cancer 80: 90 (P247)

Kanwar JR, Kanwar RK, Pandey S, Ching LM, Krisansen GW (2001) Vascular attack by 5,6-dimethoxyxanthenone-4-acetic acid combined with B7.1 (CD80)-mediated immunotherapy overcomes immune resistance and leads to the eradication of large tumors and multiple tumor foci. Cancer Res 61: 1948 – 1956

Kaye SB, Clavel M, Dodion P, Monfardini S, ten Bokkel Huink WW, Wagener DT, Gundersen S, Stoter G, Smith J, Renard J, Vlangalbeke M, Cavalli F (1990) Phase-II trials with flavone acetic acid (NSC-347512, LM975) in patients with advanced carcinoma of the breast, colon, head and neck and melanoma. Invest New Drugs 8: 595 – 599

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Kerr DJ, Kaye SB (1989) Flavone acetic acid—preclinical and clinical activity. Eur J Cancer Clin Oncol 25: 1271 – 1272
Kerr DJ, Kaye SB, Cassidy J, Bradley C, Rankin E, Adams L, Setanoians A, Young T, Forrest G, Soukop M, Clavel M (1987) Phase I and pharmacokinetic study of flavone acetic acid. Cancer Res 47: 6766 – 6781
Kestell P, Zhao L, Jameson MB, Stratford MR, Folkes LK, Baguley BC (2001) Measurement of plasma 5-hydroxyindoleacetic acid as a possible clinical surrogate marker for the action of antiangiogenic agents. Clin Chim Acta 314: 159 – 166
Kligfield P, Lax KG, Okin PM (1996) QT interval—heart rate relation during exercise in normal men and women: definition by linear regression analysis. J Am Coll Cardiol 28: 1547 – 1555
Lash CJ, Li AE, Rutland M, Baguley BC, Zwi LJ, Wilson WR (1998) Enhancement of the anti-tumour effects of the antivascular agent 5,6-dimethylxanthene-4-acetic acid (DMXAA) by combination with 5-hydroxytryptamine and bioreductive drugs. Br J Cancer 78: 439 – 445
Lejeune FJ, Ruegg C, Liendard D (1998) Clinical applications of TNF-alpha in cancer. Curr Opin Immunol 10: 573 – 580
Lew YS, Brown SL, Griffin RJ, Song CW, Kim JH (1999) Arsenic trioxide causes selective necrosis in solid murine tumors by vascular shutdown. Cancer Res 59: 6033 – 6037
Marmor MF, Kessler R (1999) Sildenafil (Viagra) and ophthalmology. Surv Ophthalmol 44: 153 – 163
Murata R, Overgaard J, Horsman MR (2001) Comparative effects of combined radioimmunotherapy and antivascular drugs by the antivascular agent 5,6-dimethylxanthene-4-acetic acid (DMXAA), a novel antivascular agent. Cancer Chemother Pharmacol 48: 159 – 165
O’Dwyer PJ, Shoemaker D, Zaharko S, Grieshaber C, Plowman J, Corbett T, Old LJ (1985) Tumor necrosis factor (TNF). Science 228: 1192 – 1194
Oliver IN, Webster LK, Bishop JF, Stokes KH (1992) A phase I and pharmacokinetic study of 12-h infusion of flavone acetic acid. Cancer Chemother Pharmacol 29: 354 – 360
Otto F, Schmid P, Mackensen A, Wehr U, Seiz A, Braun M, Galanos C, Mertelsmann R, Engelhardt R (1996) Phase II trial of intravenous endotoxin in patients with colorectal and non-small cell lung cancer. Eur J Cancer 32A: 1712 – 1718
Pedley RB, Boden JA, Boden R, Boxer GM, Flynn AA, Keep PA, Bergent RH (1996) Ablation of colorectal xenografts with combined radioimmunotherapy and tumor blood flow-modifying agents. Cancer Res 56: 3292 – 3300
Pedley RB, Sharma SK, Boxer GM, Boden R, Stribbling SM, Davies L, Springer CJ, Bergent RH (1999) Enhancement of antibody-directed enzyme prodrug therapy in colorectal xenografts by an antivascular agent. Cancer Res 59: 3998 – 4003
Philpott M, Baguley BC, Ching LM (1995) Induction of tumour necrosis factor-α by single and repeated doses of the antitumour agent 5,6-dimethylxanthene-4-acetic acid. Cancer Chemother Pharmacol 36: 143 – 148
Philpott M, Joseph WR, Crosier KE, Baguley BC, Ching LM (1997) Production of tumour necrosis factor-alpha by cultured human peripheral blood leucocytes in response to the anti-tumour agent 5,6-dimethylxanthene-4-acetic acid (NSC 640488). Br J Cancer 76: 1586 – 1591
Pruinij FB, van Daalen M, Holford NH, Wilson WR (1997) Mechanisms of enhancement of the antitumour activity of melphalan by the tumour-blood-flow inhibitor 5,6-dimethylxanthene-4-acetic acid. Cancer Chemother Pharmacol 39: 541 – 546
Riewcastle GW, Atwell GJ, Li ZA, Baguley BC, Denny WA (1991) Potential antitumor agents. 61. Structure—activity relationships for in vivo colon 38 activity among distibuted 9-oxo-9H-xanthene-4-acidic acids. J Med Chem 34: 217 – 222
Riewcastle GW, Kestell P, Baguley BC, Denny WA (1990) Light-induced breakdown of flavone acetic acid and xanthene analogues in solution. J Natl Cancer Inst 82: 528 – 529
Rubin J, Ames M, Schutt AJ, Nichols WL, Bowie EJ, Kovach JS (1987) Flavone-8-acetid inhibits tiostitin-induced platelet aggregation and prolongs bleeding time. Lancet 2(8657): 1081
Ruegg C, Yilmaz A, Bieler G, Barnatova E, Lohfert P, Lejeune FJ (1998) Evidence for the involvement of endothelial cell integrin alphaVbeta3 in the disruption of the tumor vasculature induced by TNF and IFN-gamma. Nat Med 4: 408 – 414
Rustin GJ, Galbraith SM, Taylor NJ, Maxwell R, Tozer G, Baddeley H, Wilson I, Prise V (1999) Combretastatin A4 phosphate (CA4P) selectively targets vasculature in animal and human tumors. Clin Cancer Res 5: 14
Rustin GJ, Bradley C, Galbraith S, Stratford M, Loadman P, Waller S, Bellenger K, Gumbrell L, Folkes L, Halbert G (2003) 5,6-Dimethylxanthene-4-acetic acid (DMXAA), a novel antivascular agent: phase I clinical and pharmacokinetic study. Br J Cancer 88: 1160 – 1167
Siim BG, Lee AE, Shalal-Zwain S, Pruinij FB, McKeage MJ, Wilson WR (2003) Marked potentiation of the antitumour activity of chemotherapeutic drugs by the antivascular agent 5,6-dimethylxanthene-4-acetic acid (DMXAA). Cancer Chemother Pharmacol 51: 43 – 52
Siim BG, Pruinij FB, Shalal-Zwain S, McKeage MJ, Wilson WR (2002) Marked potentiation of the antitumour activity of chemotherapeutic drugs by the antivascular agent 5,6-dimethylxanthene-4-acetic acid (DMXAA). Cancer Chemother Pharmacol
Smith GP, Calveley SB, Smith MJ, Baguley BC (1987) Flavone acetic acid (NSC 347512) induces haemorrhagic necrosis of mouse colon 26 and 38 tumours. Eur J Cancer Clin Oncol 23: 1209 – 1211
Speeg K (1995) The serotonin syndrome: an update on the management of serotonin-associated drug reactions. J Clin Psychiatry 56: 10
Stucker O, Vicaut E, Teisseire B (1992) Specific response to 5-HT2 agonists by arterioles linked to Meth A tumors in mice. Am J Physiol 262: H704 – H709
Van de Kar LD, Rittenhouse PA, Li Q, Levy AD (1996) Serotonergic regulation of renin and prolatin secretion. Behav Brain Res 73: 203 – 208
Wallis RM, Leishman D, Pullman L, Graepel P, Heywood R (1998) Effects of sildenafil on retinal histopathology and electoretinogram (ERG) in dogs. Opsphinic Res 38: 568
Weiss RB, Green RF, Edelman BD, Collins JM, Pelosi JJ, Sulkes A, Curt GA (1999) Phase I and clinical pharmacology study of intravenous flavone acetic acid (NSC 347512). Cancer Res 48: 5878 – 5882
Wilson WR, Baguley BC (2000) Combination of the antivascular agent DMXAA with radiation and chemotherapy. Int J Radiat Oncol Biol Phys 46: 706
Wilson WR, Li AE, Cowan DS, Siim BG (1998) Enhancement of tumor radiation response by the antivascular agent 5,6-dimethylxanthene-4-acetic acid. Int J Radiat Oncol Biol Phys 42: 905 – 908
Zwi LJ, Baguley BC, Gavin JB, Holdaway KM, Wilson WR (1992) The role of immune effector cells in flavone acetic acid-induced injury to tumor cells in EMT6 spheroids. Oncol Res 4: 333 – 339
Zwi LJ, Baguley BC, Gavin JB, Wilson WR (1989) Blood flow failure as a major determinant in the antitumor action of flavone acetic acid (NSC 347512). J Natl Cancer Inst 81: 1005 – 1013
Zwi LJ, Baguley BC, Gavin JB, Wilson WR (1990) Necrosis in non-tumour tissues caused by flavone acetic acid and 5,6-dimethylxanthene acetic acid. Br J Cancer 62: 932 – 934