5,6-Dimethylxanthenone-4-Acetic Acid in the Treatment of Refractory Tumors: a Phase I Safety Study of a Vascular Disrupting Agent

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The role of vascular targeting agents in the treatment of solid tumors is attracting considerable research interest—in particular, vascular disrupting agents (VDA) that target the existing tumor vasculature, and their potential as components of combination therapy. Four small-molecule VDAs are under clinical investigation: the tubulin-depolymerizing VDAs combretastatin A4, ZD6126, and AVE8062A, and the microtubule-dependent VDA 5,6-dimethylxanthenone-4-acetic acid (DMXAA) (1). Although VDAs are showing promise in clinical trials, some have been associated with cardiovascular adverse events (2).

DMXAA was developed by the Auckland Cancer Society Research Centre in a program to synthesize more effective analogues of flavone-8-acetic acid—a compound with exceptional activity against a range of transplantable murine tumors with established vasculatures (3–5), but which was inactive in clinical trials (6). DMXAA mimics the effects of flavone-8-acetic acid (7–10), but is more active and has a 12-fold higher potency as a biological response modifier and antitumor agent in murine tumor models (11). Furthermore, unlike flavone-8-acetic acid (12, 13), DMXAA induces human immune cells to produce tumor necrosis factor-α (TNF-α), which is known to cause hemorrhagic necrosis in tumors (14, 15).

In animal tumor models, DMXAA has been shown to act synergistically with radiotherapy (16), chemotherapy (particularly taxanes; refs. 17–20), bioreductive cytotoxic drugs (21, 22), radioimmunotherapy (23), antibody-directed enzyme pro-drug therapy (24), thalidomide (25), and immunotherapy (26).

In two phase I trials by Cancer Research UK in the United Kingdom (27) and New Zealand (28), 109 patients received DMXAA at doses of 6 to 4,900 mg m⁻², given i.v. over 20 minutes, either once a week or once every three weeks. Two unconfirmed partial responses were reported at doses of 1,100 and 1,300 mg m⁻², and 28 patients had a best response of stable disease. DMXAA did not cause myelosuppression, and was well tolerated at low doses. Rapidly reversible, dose-limiting toxicities were seen at 4,900 mg m⁻², including confusion, tremor, slurred speech, visual disturbance, anxiety, urinary incontinence, and
possible left ventricular failure. The maximum tolerated dose for DMXAA was therefore established at 3,700 mg m$^{-2}$.

In the New Zealand study, transient prolongation of the heart rate–corrected QT (QTc) interval was noted in patients receiving DMXAA ≥2,000 mg m$^{-2}$ (median prolongation, 52 milliseconds; range, 38-100 milliseconds). The median time to maximum prolongation was 20 minutes (range, 10-90 minutes from the onset of infusion). All patients remained asymptomatic with no evidence of serious cardiac arrhythmias on Holter monitoring, and most measurements returned to normal within 6 hours of the end of the infusion. ECG monitoring post-infusion was only conducted at higher dose levels after minor changes in heart rate were observed.

The rapid onset of visual disturbance (blurring, flickering, alteration of color discrimination, and mild photosensitivity) was also noted in the U.K. and New Zealand studies. These effects seemed to be dose-dependent, with a threshold effect within 6 hours of the end of the infusion. ECG monitoring with no evidence of serious cardiac arrhythmias on Holter monitoring indicated the DMXAA dose, to ensure double blinding. Exposure of DMXAA to sunlight was avoided to prevent decarboxylation of the triplet-state form (29). DMXAA was formulated as 86.4 mmol of 1 solution in 0.11% w/w Tris-HCl and a 200 mg mL$^{-1}$ solution in 0.11% w/w Tris-HCl, stored in darkness at room temperature in 10 mL amber vials, diluted to 50 mL with water for injection, placed in a 50 mL opaque syringe and administered as a 20-minute i.v. infusion using a rate-controlled pump and opaque tubing.

If a DMXAA dose caused QTc interval prolongation >520 milliseconds in men or 540 milliseconds in women, or any other severe toxicity, all subsequent planned higher doses were replaced with the next lowest dose to that causing the toxicity; subsequent lower doses were unaltered. If a patient experienced a dose-capping QTc interval prolongation at DMXAA 300 mg m$^{-2}$, they were withdrawn. If a patient had received a dose of DMXAA 1 week previously, and their baseline QTc interval at the subsequent visit was prolonged above inclusion criteria limits, the next DMXAA dose could be delayed by ≥2 weeks if the QTc interval fell to below those limits. To be eligible for further treatment cycles, all drug-related toxicities (other than alopecia) had to have recovered to grade 1 (≤3-week delay was permitted). Doses were also capped for neutrophil nadir ≤0.5 × 10$^9$ L$^{-1}$, platelet nadir ≤25 × 10$^9$ L$^{-1}$, increase in neurotoxicity of two grades over baseline (other than transient nonischemic events that resolved within 6 hours of infusion), or grade 3/4 nonhematologic toxicity (excluding alopecia and nausea).

**Patient assessments.** Screening assessments were done within 4 weeks before the start of treatment, with the exception of blood samples to assess eligibility, which were taken within 1 week before the start of treatment. Screening assessments were comprised of a complete medical history and physical examination, chest X-ray, 12-lead standard ECG, laboratory tests, including a full blood count with differential, urinalysis, ophthalmic tests (standard and pattern ECG, visual acuity, color discrimination tests, and fundoscopy), WHO performance status and radiological assessment of disease (computed tomography/MRI) and DCE-MRI. On the day before the administration of each dose, the following assessments were done: vital signs, 12-lead ECG [at t = −20, −10, 0 (start of infusion), 10, 20, and 30 minutes and 1, 2, 4, 6, 8, 12, and 24 hours, starting at 10:00 hours], laboratory tests, 24-hour urine collection and DCE-MRI. On the day of each dose, the following assessments were done: vital signs, 12-lead ECG [at t = −20, −10, 0 (start of infusion), 10, 20, and 30 minutes and 1, 2, 4, 6, 8, 12, and 24 hours, starting at 09:40 hours], adverse events, collection of blood samples for pharmacokinetic and pharmacodynamic analyses (at t = 0 and 20 minutes, and 1, 2, 4, 8, 12, and 24 hours), and 24-hour urine collection. Following these assessments, and a 24-hour period of continuous ECG safety monitoring, the DCE-MRI was repeated (26 ± 2 hours after dosing).

Patients attended a follow-up visit 2 to 4 weeks after the last dose of DMXAA, when the following assessments were done: physical examination, adverse events, laboratory tests, urinalysis, and ophthalmic tests.

The mean QT interval was obtained from the 12-lead ECGs at each time point and was corrected for heart rate. Three “standard” methods of correction were investigated, i.e., Bazett (QTc = QT/V($R$-R interval)), Fridericia (QTc = QT/V($R$-R interval)), and Framingham (QTc = QT + 0.154 × (1 − preceding R-R interval)), and a study-specific linear adjustment [QTc = QT + b × (1 − preceding R-R interval)]; where b is the within-patient regression slope of the QT/R relationship based on the approach of Van de Water (30). For each
Changes in QTc interval from profile baseline were adjusted for pre-dose baseline (the average of the three QTc intervals calculated from the 12-lead ECGs taken at $t = -20, -10$, and 0 minutes on the day of dosing). The mean changes in QTc interval from profile baseline at each time point, and the mean maximum changes (and 95% confidence intervals) in QTc interval from profile baseline over 24 hours were calculated for each dose. Individual uncorrected QT intervals that exceeded 500 milliseconds and QTc intervals that exceeded sex-specific limits (>450 milliseconds for men and >470 milliseconds for women) were regarded as being prolonged, as were increases in QTc interval from profile or pre-dose baseline of >30 and >60 milliseconds (CPMP/986/96 document). The relationship between the QTc interval (Bazett correction) and DMXAA plasma concentrations was investigated using the Pearson product-moment correlation coefficient.

All AUC calculations employed the trapezoidal rule, and were based on actual rather than scheduled timings. The relationships between DMXAA dose and AUC $(0-24)$ hours for 5-HIAA plasma and urine concentrations and TNF-α plasma concentrations, and between DMXAA dose and AUC (0-260) minutes for systolic blood pressure, diastolic blood pressure, and heart rate were analyzed by analysis of covariance. For ophthalmologic assessments, changes before and after a dose of DMXAA were analyzed with the Wilcoxon matched pairs test, using data for each eye.

For tumor blood flow, a standard compartmental model (32) was used to describe the arterial influx of gadopentetate dimeglumine into the tumor extravascular extracellular space and its venous efflux. Vascular parameters were derived by applying the multi-compartmental model analysis to the tissue gadolinium concentration-time curve (33). Quantitative modeling variables were derived, including transferconstant($K_{\text{trans}}$), rateconstant($k_{\text{ep}}$), tissueleakagespace($V_{\text{L}}$), ($V_{\text{e}}$), and area under the gadopentetate dimeglumine curve at 60 seconds (34). DCE-MRI tumor measurements were not normalized for arterial or normal tissue blood flow. Responses were analyzed on

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a patient-by-patient and group basis for each dose, making the explicit assumption that previous doses of DXMAA left no residual vascular effects.

Results

**Patient characteristics.** Fifteen eligible patients were enrolled and received study medication; baseline characteristics and previous therapy are summarized in Table 1. The study population comprised all randomized patients. Fourteen patients completed the study, receiving six doses of DMXAA each, and one patient was withdrawn after receiving four doses of DMXAA (death due to malignant disease). All patients received the intended dose on each treatment occasion. For one patient, the dose was capped following the 3,000 mg m$^{-2}$ dose. Because the remaining doses were all below the capped dose, this patient still received all six doses.

**Prolongation of QTc interval.** The study-specific QT correction produced a mean regression slope of the QTc:R-R relationship of zero. Both the Fridericia and Framingham corrections produced mean slopes that were not significantly different from zero, but the Bazett method overcorrected significantly ($P < 0.0001$). The study-specific QT correction was therefore regarded as most appropriate for interpretation of QT data. For this correction [$\text{QTc} = \text{QT} + b \times (1 - \text{preceding R-R interval})$, where $b$ is the within-patient regression slope of the QT:R-R relationship] $b$ was calculated to be 0.159.

Figure 1A shows the estimated mean maximum change in QTc interval from profile baseline; statistically significant increases of 9.5 milliseconds ($P < 0.01$) and 7.7 milliseconds ($P < 0.05$) were seen after doses of 2,400 and 3,000 mg m$^{-2}$ DMXAA, respectively. The greatest effect was seen with the 2,400 mg m$^{-2}$ dose; at this level, the mean increase in QTc interval from profile baseline was statistically significant ($P < 0.01$) at $t = 10, 20,$ and 30 minutes, and at 1 hour (Fig. 1B).

No individual uncorrected QT interval exceeded 500 milliseconds and only two individual QTc intervals exceeded sex-specific limits (after 2,400 mg m$^{-2}$ of DMXAA). There were 16
instances when the increase in QTc interval from pre-dose baseline exceeded 30 milliseconds (60% after 2,400 or 3,000 mg m⁻²), and 15 instances when the increase in QTc interval from profile baseline exceeded 30 milliseconds (73% after 2,400 or 3,000 mg m⁻²). No increase in QTc interval from pre-dose baseline exceeded 60 milliseconds, but there were three instances when the increase in QTc interval from profile baseline exceeded 60 milliseconds (one each after 1,200, 1,800, and 2,400 mg m⁻²).

**Adverse events.** A total of 460 adverse events were reported—most frequently infusion site pain, visual disturbance, nausea, headache, altered taste, and tumor pain (Table 2). The number of events increased with DMXAA dose (44 events after 300 mg m⁻² compared with 127 after 3,000 mg m⁻²), and there seemed to be a dose-related increase in reports of nervous system, gastrointestinal, and eye disorders. Most events were classified as mild (76% of 137 classified) or CTC grades 1 or 2 (92% of 323 classified). There were a total of 28 adverse events in seven subjects graded as “severe” or CTC grades 3 or 4. Their relationship to the study drug was 0 for 9 events, remote for 11 events, possible for 6 events, and probable for 2 events. Of the eight severe, grade 3 or 4 adverse events with a possible or probable causal relationship to DMXAA, there were four episodes of exacerbation of tumor pain, two episodes of visual disturbance, and one episode each of headache and depression. All but one of these had resolved or improved within 1 day of onset.

Severity increased with DMXAA dose and there was a general trend for the relatedness of adverse events to study medication to increase with DMXAA dose. There were no deaths due to study medication.

Twenty-four cardiac events were reported in seven patients, all grades 1 or 2. Sinus tachycardia was most frequent (13 events in four patients), followed by sinus bradycardia (8 events in one patient) and possible myocardial ischemia (2 events in two patients). There was no evidence of a dose effect for either tachycardia or bradycardia, with a similar number of events reported at most doses. Two patients at the two highest doses had ECGs that showed ST segment and T wave changes suggestive of possible myocardial ischemia, both CTC grade 2. In all cases, there were no clinical signs or symptoms of myocardial ischemia and the plasma concentration of troponin-I was below the detection level (0.2 µg L⁻¹).

DMXAA produced dose-dependent increases in systolic and diastolic blood pressure, peaking 20 minutes post-dose (mean increases of 30.2 and 17.3 mm Hg, respectively, after the highest DMXAA dose; Fig. 2A and B). Increases in heart rate at 20 minutes post-dose were only observed after the two highest DMXAA doses (mean increases of 3.4 and 9.4 bpm, respectively; Fig. 2C). Significant relationships were found between DMXAA dose and AUC (0-260 minutes) for systolic blood pressure (P = 0.009), diastolic blood pressure (P = 0.005), and heart rate (P = 0.02).

Twelve patients completed the pretreatment and posttreatment ophthalmic assessments. No consistent abnormality was induced by DMXAA, and several patients had no identifiable variation between their paired tests. In particular, visual acuity, contrast sensitivity, color contrast sensitivity, and dark adaptation did not change significantly.

For electrodiagnostic variables, some data points were unmatched because some patients had only one eye tested and one patient did not have post-dose follow-up. Small changes were detected in some electrodiagnostic tests, which were significant in the whole group analysis [bright flash-a-wave implicit time, P = 0.022; bipolar on-response (b-wave); P = 0.047].

**Pharmacokinetic/pharmacodynamic analyses.** The Cmax and AUC0-24 for free and total DMXAA plasma concentration increased nonlinearly with increasing DMXAA doses (Fig. 3). The correlation coefficient between free DMXAA plasma concentration and QTc interval was significant (P < 0.05) at all 10 post-dose time points in which ECG readings were taken. The correlation coefficient between total DMXAA plasma concentration and QTc interval was significant (P < 0.05) at t = 20 minutes, 30 minutes, and 24 hours post-dose.

Peak mean plasma concentrations of 5-HIAA were reached 20 minutes and 2 hours post-dose for the 300 and 600 mg m⁻² dose groups, respectively, and at 4 hours post-dose for the other dose groups (Fig. 4A). The maximum increase in mean 5-HIAA
plasma concentration from pre-dose baseline was 9.1, 28.6, 52.9, 65.3, 59.1, and 73.5 \( \mu g \) L\(^{-1}\) in the 300, 600, 1,200, 1,800, 2,400, and 3,000 \( \text{mg m}^{-2}\) dose groups, respectively, and a significant correlation was observed with the \( C_{\text{max}} \) for total plasma DMXAA \( (P = 0.001; \text{Fig. 4B}) \) but not for free plasma DMXAA \( (P = 0.08) \). The relationship between AUC \( (0,24 \text{ hours}) \) for 5-HIAA plasma concentration and DMXAA dose was significant \( (P < 0.001) \). There were no obvious trends for the urine concentration of 5-HIAA, or for the concentration of TNF-\( \alpha \) in plasma or urine.

Quantitative DCE-MRI provided no evidence of significant reductions in tumor kinetic enhancement variables related to perfusion and permeability. No significant changes in \( K_{\text{trans}} \) or \( k_{\text{ep}} \) were seen in individual patients at any dose, but a significant \( (P < 0.05) \) increase in \( K_{\text{trans}} \) was seen in the 2,400 \( \text{mg m}^{-2}\) dose group. Significant \( (P < 0.05) \) increases in \( V_e \) were seen in six patients (one at 300, four at 1,200, and one at 2,400 \( \text{mg m}^{-2}\)), and in the 1,200 \( \text{mg m}^{-2}\) dose group. A general, nonsignificant increase in the area under the gadopentetate dimeglumine curve was observed.

**Discussion**

In this phase I safety study of DMXAA in the treatment of refractory tumors, dose order and period-effect bias were reduced by the use of a crossover Latin squares design. Although this approach resulted in two patients receiving the highest dose first, all doses had been given in earlier phase I studies and the maximum dose was lower than the maximum tolerated dose \( (27, 28) \). Crossover designs are usually more powerful than parallel designs in distinguishing differences between treatments, because within-patient variability is generally less than between-patient variability \( (35) \); the most important disadvantage is potential for carry-over effects \( (36) \). However, the use of confidence intervals in assessing differences ensures that any such reduction in statistical power does not lead to incorrect interpretations. Furthermore, this study design incorporated washout periods to reduce the likelihood of carry-over effects and the half-life of DMXAA is 8.1 ± 4.3 hours \( (27) \). From a practical perspective, the crossover design was more efficient and generated more pharmacokinetic/pharmacodynamic data at each dose level than conventional phase I oncology trial designs.

A dose-related mean increase in QTc interval was observed at the two highest doses of DMXAA \( (2,400 \text{ and } 3,000 \text{ mg m}^{-2}) \), but was limited to a short period immediately after infusion. This result was supported by the analysis of outlier data and the pharmacokinetic relationship between DMXAA plasma concentration and QTc interval, and correlates well with previous findings \( (28) \). There were no cardiac arrhythmias or dose-limiting QTc prolongation, except for one episode of sinus pause of short duration (2-3 seconds) that was asymptomatic, uncomplicated, and resolved spontaneously. The use of DMXAA doses \( \leq 1,800 \text{ mg m}^{-2}\) in future clinical trials should ensure that patient safety in general will not be compromised, although individual patients may remain at risk of significant, albeit transient, QTc prolongation.

DMXAA had only transient and tolerable adverse effects, which were similar to those reported in previous phase I studies but dissimilar to those associated with cytotoxic chemotherapy. The number of events reported increased with DMXAA dose, but most were classified as mild or CTC grades 1 or 2, even at the higher doses. In particular, no major hematologic or biochemical toxicities occurred.

Cardiovascular adverse events \( (n = 24) \) were classified as CTC grades 1 to 2, and included two instances of reversible myocardial ischemia (at the two highest doses). In both cases, there were ST segment and T wave ECG changes without clinical signs or symptoms of cardiac ischemia and the plasma concentration of troponin-I was below the level of detection, indicating that DMXAA did not cause myocardial necrosis.
DMXAA induced acute changes in arterial blood pressure and heart rate, which were reversible, dose-dependent, and related to AUC. Similar effects have been seen with other VDAs, including combretastatin A4 (2, 37). The changes in blood pressure indicate a systemic vascular effect of DMXAA, although it is not yet clear whether this is a direct effect or mediated by central nervous system mechanisms. The initial increase in blood pressure might be due to increased systemic vascular resistance, although the hot flush and warm peripheries seen after DMXAA infusion would argue against this. The increase and subsequent decrease in blood pressure coincided with the peak and decrease in DMXAA plasma concentration. Reductions in blood pressure might be the effect of compensatory mechanisms. With regard to heart rate, the underlying mechanism is unclear, but may be a compensatory response to changes in hemodynamic or central variables such as pain and temperature.

As in other phase I studies, transient visual disturbances were reported after DMXAA administration, which were dose-related. Some of the ERG effects were consistent with previous acute observations, notably increased a-wave implicit time for both scotopic and photopic responses (28). Detailed ophthalmic assessments undertaken 2 weeks after the last DMXAA dose provided no clear evidence of clinically significant cumulative ophthalmic toxicity. Small changes detected statistically in some electrodiagnostic tests were insufficient to manifest as a noticeable subjective change in visual function. Whether these electrodiagnostic changes could herald a possible cumulative effect of DMXAA or potential risk in patients with preexisting retinal (particularly macular) pathology is not known.

The nonlinear (dose-dependent) pharmacokinetic profile of DMXAA in this study is consistent with that observed previously in mice and humans (27, 38). At the maximum tolerated dose in the mouse, the $C_{\text{max}}$ and AUC for total and free DMXAA plasma concentrations were $\sim 170 \, \mu g/mL$, $677 \, \mu g/mL\cdot h$, $6 \, \mu g/mL$, and $23.7 \, \mu g/mL\cdot h$, respectively (38). These preclinical plasma concentrations and exposures are similar to those achieved at doses of 1,200 to 1,800 mg/m$^2$ in patients in the current trial, suggesting that plasma DMXAA concentrations within the preclinical therapeutic range are readily achievable clinically. With regard to pharmacodynamics, increases in plasma concentration of 5-HIAA (a vascular damage biomarker) correlated with DMXAA dose, and were near maximum at DMXAA doses $\geq 1,200 \, \text{mg} \cdot \text{m}^{-2}$. In a previous study (27), there was a dose-dependent increase in the 5-HIAA plasma concentration at DMXAA doses $\geq 650 \, \text{mg} \cdot \text{m}^{-2}$, which became more marked in extent and duration as the DMXAA dose increased. The reason for this disparity between the studies is not clear.

Fig. 3. Mean $C_{\text{max}}$ and AUC$_{0-24}$ for free (A and C) and total (B and D) DMXAA plasma concentrations, for each DMXAA dose (bars, 95% confidence interval).
Although DMXAA may act through release of TNF-α in the tumor vasculature, there was no obvious increase in the TNF-α plasma concentration in this study. This is broadly consistent with the earlier phase I studies in which no reproducible increases above pre-dose values were seen (27, 28), and with murine data showing that the predominant effect of DMXAA on TNF-α is on intratumoral production (39).

With regard to tumor blood flow, a reduction in \( K_{\text{trans}} \) would be anticipated with VDAs such as DMXAA, if significant antivascular effects were occurring at the time of the DCE-MRI examination. Such an effect has been observed in both xenografts and in humans with the VDA combretastatin (40, 41), and was particularly marked 4 hours post-dose, with lesser effects 24 hours post-dose. In this study, however, quantitative DCE-MRI provided little evidence of an antivascular effect 26 hours after DMXAA dose. The significant increases seen in \( K_{\text{trans}} \) in the cohort analysis of DMXAA 2,400 mg m\(^{-2}\) are consistent with increased vascular permeability, possibly due to cytokine release and enhanced cell-mediated cytotoxicity induced by DMXAA. The changes in \( V_e \) seen in individual patients and in the cohort analysis of DMXAA 1,200 mg/m\(^2\) may also share this underlying cause, and are potentially indicative of changes in tumor cellular density or necrosis (42).

A possible explanation of our findings is that the antivascular effect measured by DCE-MRI occurred during the first hours of DMXAA administration, and had disappeared within 24 hours. This hypothesis is supported by the hemodynamic effects seen in the first 4 hours after DMXAA administration and the corresponding peak of DMXAA plasma concentration. However, it is inconsistent with data from the only other study to have examined the effects of DMXAA using DCE-MRI, in which reductions in enhancement characteristics, in keeping with vascular shutdown, were observed 4 and 24 hours after DMXAA dose (43). The quantitative DCE-MRI modeling done in this study was not undertaken in the previous study.

In conclusion, on the basis of the findings of this phase I safety study, the proposed doses of DMXAA for further clinical studies are 1,200 and 1,800 mg m\(^{-2}\), with a recommendation for continued assessment of QTc interval prolongation, cardiac ischemia and visual disturbances. These doses had minimal effects on the QTc interval in most patients, produced near-maximum responses of the vascular damage biomarker 5-HIAA, achieved DMXAA plasma concentrations within the preclinical therapeutic range, and were well tolerated. A phase II program to investigate DMXAA in combination therapy is ongoing; studies are evaluating DMXAA in combination with carboplatin and paclitaxel in non–small cell lung and ovarian cancers, and in combination with docetaxel in prostate cancer.

Acknowledgments

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