

Phase I Trial of XR9576 in Healthy Volunteers Demonstrates Modulation of P-glycoprotein in CD56⁺ Lymphocytes after Oral and Intravenous Administration

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ABSTRACT

XR9576 is a novel inhibitor of P-glycoprotein (P-gp) that has been shown to reverse P-gp-dependent multidrug-resistance in tumor cell lines and tumor-bearing animals. Here we report the first i.v. and p.o. administration to healthy volunteers of XR9576 in dose-escalating studies with the aim of investigating its effects on safety, its pharmacokinetics, and a surrogate marker of efficacy. XR9576 was administered as a single dose-upward titration of 0.1, 0.2, 0.5, 1.0, and 2 mg/kg XR9576 i.v. or 50, 100, 200, 500, and 750 mg/volunteer p.o. The surrogate marker for *in vivo* efficacy examined the accumulation of the P-gp substrate Rhodamine-123 (Rh-123) in P-gp-expressing CD56⁺ lymphocytes by flow cytometry. Addition of Rh-123 to blood samples from subjects given XR9576 or a placebo demonstrated drug-dependent modulation of P-gp activity. Even at the lowest doses, significant effects were observed on Rh-123 accumulation in CD56⁺ cells. Maximal effects were seen during the i.v. infusion or 4–6 h after oral administration. As the dose was increased, a concomitant rise in the level and duration of P-gp blockade was observed. A dose of 2.0 mg/kg i.v. and ≥200 mg/volunteer p.o. gave ~100% inhibition of P-gp for in excess of 24 h. All doses of XR9576 were well tolerated. Inhibition increased with XR9576 plasma concentration, and maximal activity was achieved at 150–200 ng/ml XR9576. In conclusion, XR9576 has demonstrated sustained inhibition of P-gp after i.v. and oral administration and, supported by the elimination half-life of about 24 h, XR9576 is being taken into Phase II as a once-daily agent.

INTRODUCTION

MDR² attributable to the overexpression of P-gp is known to develop in a wide variety of tumor types and significantly attenuates the efficacy of many commonly used chemotherapeutic agents (*e.g.*, doxorubicin and paclitaxel; Ref. 1). Expression

of P-gp has been linked to MDR in both intrinsically resistant tumors and in those that acquire the resistant phenotype during treatment (2). P-gp is a member of the ATP-binding cassette superfamily and acts as an efflux pump to reduce the intracellular concentrations of cytotoxics (2).

Significant improvement has been made since it was discovered that first-generation inhibitors, originally designed for targets other than P-gp (*e.g.*, the calcium channel blocker verapamil) had unacceptable toxicities in clinical studies (3, 4). More recently, molecules have been designed to interact specifically with P-gp, and a number of these, including LY79553 (5) and PSC833 (6), have advanced to the clinic. PSC833 is at the most advanced stage of clinical development (Phase III) and is reported as sensitizing refractory ovarian tumors to paclitaxel (7).

XR9576, also designed as a specific P-gp modulator (Fig. 1), is a highly potent novel anthranilic acid derivative that potentiates the activity of a number of MDR-associated cytotoxics in cell lines overexpressing P-gp (8, 9). Typically it has half-maximal effects at approximately 30 nM. This *in vitro* activity translates to tumor-bearing animals where XR9576 has been shown to reverse the resistance of multidrug-resistant human xenografts at well-tolerated doses (9). XR9576 has a high affinity for P-gp ($K_d = 2.5 \pm 0.7$ nM; Ref. 10) and, importantly, has no effect on the related transporter multidrug-resistance-associated protein (8).

We report here the first i.v. and oral administration of XR9576 to healthy volunteers in two dose-escalating studies that included the use of a surrogate marker of efficacy to establish inhibition of P-gp as a pharmacological end point. As reported by Witherspoon *et al.* (11), CD56⁺ lymphocytes constitutively express significant levels of P-gp. Thus the measurement of inhibition of P-gp in CD56⁺ lymphocytes is a surrogate for the inhibition of P-gp in tumors. In this way we have demonstrated the inhibition of P-gp in lymphocytes from volunteers given XR9576 and have achieved complete inhibition for in excess of 24 h. These data have supported the selection of XR9576 doses for oral and i.v. Phase II studies.

MATERIALS AND METHODS

Clinical Study Design. The studies were rising-single-dose, randomized, double-blind, and placebo-controlled in healthy male volunteers to assess the tolerability, pharmacokinetics, and effect on a surrogate marker of efficacy of single doses of i.v.- and p.o.-administered XR9576. All volunteers gave informed consent, and study entry requirements included an age range of 18–55 years, being within 15% of the normal height for weight according to Metropolitan Life Assurance tables, and having no clinically significant abnormalities at screening. All volunteers underwent a complete medical history and examination that included the cardiovascular, respiratory, hemopoietic, central and peripheral nervous, gastrointestinal, endocrine, and renal systems. Laboratory tests included a 12-lead

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² The abbreviations used are: MDR, multidrug-resistance; P-gp, P-glycoprotein; SPE, solid phase extraction; Rh-123, Rhodamine-123; PI, propidium iodide; MCF, mean channel fluorescence.

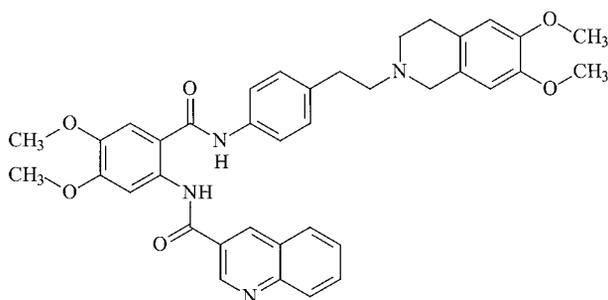


Fig. 1 Structure of XR9576.

ECG, full blood count with differential white cell and platelet counts, urea and electrolytes, liver function tests, and measurement of serum proteins, calcium, phosphate glucose, and creatinine. Panels of five subjects (four on XR9576 and one on a placebo) received single doses of the drug at the given dose-level on only one occasion. XR9576 was administered as a 250-ml i.v. infusion over 30 min (mesylate salt) or in hard gelatin capsules (free-base; 50 or 100 mg base/capsule). Blood samples were taken into heparinized Vacutainers (Becton Dickinson) at the time points shown in the results section for measurement of XR9576 plasma levels and surrogate marker activity (CD56⁺ cells).

Assay of Plasma Drug Levels. XR9576 was assayed in human plasma by a validated procedure involving SPE followed by liquid chromatography with tandem mass-spectrometric detection. Aliquots of the plasma samples (100 μ l) and an internal standard (structurally related to XR9576) were mixed and centrifuged. The supernatants, containing XR9576 and the internal standard, were extracted using OASIS HLB SPE cartridges. The eluates from the SPE cartridges, containing the analytes, were subjected to tandem mass-spectrometric detection analysis. The lower limit of quantification for XR9576 in human plasma was 2.5 ng/ml with linearity demonstrable to 1000 ng/ml. Full details of the analytical procedure will be published elsewhere.

Surrogate Marker Assay. The assay for inhibition of P-gp in CD56⁺ lymphocytes was carried out using modifications of the method published by Witherspoon *et al.* (11) Duplicate blood samples were aliquoted into polypropylene tubes (0.5 ml/tube) and processed in parallel. Predose samples were split into 4 \times 0.5 ml aliquots, two of which (duplicates) were spiked with XR9576 to a final concentration of 3.0 μ M from a 30- μ M stock in RPMI. This was incubated at 37°C for 1 h prior to addition of 55 μ l of Rh-123 (Sigma) from a 10-fold concentrated stock in RPMI/25 mM HEPES to give a final concentration of 150 ng/ml. For all other samples that were not spiked, 50 μ l of Rh-123 were added. Samples were incubated at 37°C for 1 h then chilled on ice and stored at 4°C with agitation until preparation of WBCs. Preliminary studies had confirmed that overnight storage of blood samples did not disrupt the assay (data not shown).

WBCs were prepared by dilution of the chilled blood samples with 20 volumes of erythrocyte lysis buffer [0.15 M NH₄Cl, 1 mM KHCO₃, 0.1 mM Na₂EDTA (pH 7.2–7.4), containing 0.04% sodium azide; all reagents from Sigma) at 4°C. Samples were then agitated gently for 1 h at 4°C before being centrifuged at 4°C. The cell pellet contained principally WBCs, with only minor contamination with RBCs. Cells were trans-

ferred to a 4-ml flow cytometry tube and washed twice with PBS/0.1% BSA/0.04% sodium azide (Sigma) before staining with an anti-CD56⁺ monoclonal antibody or an IgG1 isotype control (both Becton Dickinson) using conditions recommended by the supplier. After 30 min incubation on ice, cells were washed before being resuspended in 0.5 ml PBS/BSA/azide containing 1 μ g/ml PI (Sigma) to stain for dead cells.

Flow cytometry analysis was carried out using an Ortho Diagnostics flow cytometer (Cyturon Absolute) using three color detection on 65,000 total events as follows: (a) green, Rh-123; (b) orange, anti-CD56-PE; and (c) red, PI. Using a gate on the PI-negative population of lymphocytes, it was possible to measure the orange and green fluorescence only in live cells. IgG1 isotype controls were used to set a cutoff whereby Rh-123 accumulation was measured only in CD56⁺ cells. Analysis was carried out using Ortho Diagnostics Immunocount software.

Flow cytometry analysis generated data sets for the amount of green fluorescence (MCF) in the CD56⁺ population of WBCs that directly correlated with the amount of cell-associated Rh-123. The MCF was converted to percentage inhibition using the predose and the 3- μ M XR9576 (final concentration) spike controls as follows:

$$\text{Percentage inhibition} = \frac{(\text{Sample MCF}) - (\text{Predose MCF})}{(\text{Spike MCF}) - (\text{Predose MCF})} \times 100$$

All data represent the mean of duplicate points.

RESULTS

Inhibition of P-gp in CD56⁺ Cells by XR9576 *ex Vivo*.

Flow cytometry analysis of WBCs from healthy volunteers allowed simple separation of the lymphocyte population (Fig. 2A, *Gate A*) from monocytes and granulocytes. Low numbers of residual RBCs were excluded by setting a threshold on the forward and side-scatter measurements. This lymphocyte population typically contained >95% viable cells as judged by exclusion of PI (data not shown). The CD56⁺ subpopulation, visualized by addition of a phycoerythrin-conjugated antibody (*orange fluorescence*) represented 5–30% of total viable lymphocytes (Fig. 2B, *Gate C*). Significant variation in this number was seen between volunteers. Although all lymphocytes accumulated Rh-123 (*green fluorescence*), the addition of a XR9576 spike to whole blood before purification of WBCs resulted in a significant increase in the level of Rh-123 accumulation (Fig. 2D, *Gate C*). This increase was greater in the CD56⁺ population than in the remaining lymphocytes because of the higher level of P-gp in these cells.

The XR9576-dependent increase in Rh-123 accumulation was shown to be dose-dependent by addition of the modulator at various concentrations (3–3000 nM) to whole blood (Fig. 3). Rh-123 fluorescence levels were converted to a relative measure of P-gp inhibition as described in “Materials and Methods.” This demonstrated clear inhibition of P-gp activity by XR9576 with half-maximal effect at approximately 30 nM over a number of experiments using blood from different volunteers.

Inhibition of P-gp after i.v. Administration of XR9576.

XR9576 was administered as a 30-min i.v. infusion and resulted in significant inhibition of P-gp even at the lowest doses tested (0.1 mg/kg; Fig. 4). At this dose level, data were only gathered on four volunteers (three on XR9576 and one on a placebo).

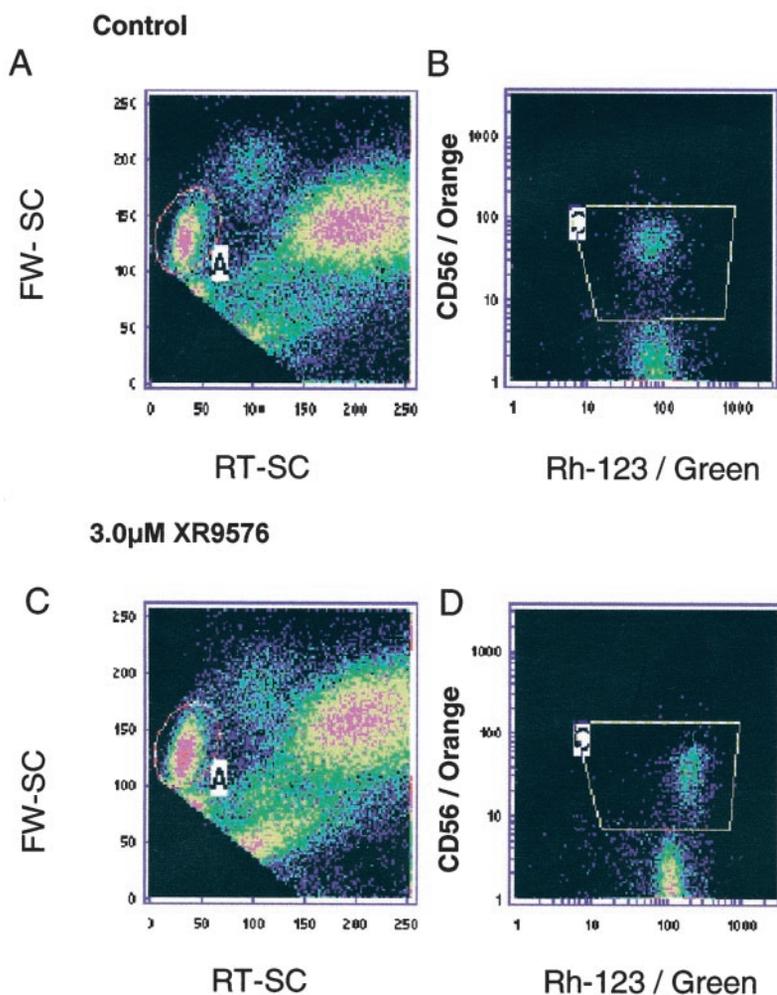


Fig. 2 Flow cytometry analysis of Rh-123 uptake in CD56⁺ lymphocytes. As detailed in “Materials and Methods,” lymphocytes were prepared by erythrocyte lysis after preincubation with Rh-123. Cells were then stained with an anti-CD56 antibody before addition of PI and analysis by flow cytometry. *A*, forward scatter versus right-hand scatter allows for selection of the lymphocyte population in *Gate A*. A cutoff (*bottom left-hand corner*) is set to exclude any residual erythrocytes. Of 55,543 total events, 4,740 were gated. *B*, PI-staining of the 4,740 gated events. All those events to the *left* of the vertical line were classed as PI-negative and, therefore, live cells. A few dead cells are seen to the *far right* of the graph. *C*, dual-color analysis allows separation of 1,133 cells staining positive (*orange*) for CD56 in *Gate C* from those which showed no staining. Note that all cells show significant *green* fluorescence, indicating significant uptake of Rh-123 by both CD56-positive and -negative cells. *D*, a histogram of the Rh-123 fluorescence of those cells from *Gate C* allows calculation of the MCF.

Subject 1 received a placebo and showed minimal fluctuation in basal Rh-123 accumulation. Subjects 2–4 were given XR9576 and significant blockade of P-gp activity was seen in their CD56⁺ cells. Maximal inhibition in this cohort (range, 78–92%; mean, 83% ± 6.3 SD) was seen during the infusion period, after which the inhibition dropped to 40% of maximum at 1 h followed by a decline between 2 and 6 h. P-gp inhibition was still evident at 6 h post-dose (range, 16–40%; mean, 24.5% ± 12.9). Additional time points to 24 h were collected for subsequent dose levels.

As the dose of XR9576 was increased from 0.1 mg/kg (Fig. 5) greater effects on Rh-123 accumulation in CD56⁺ cells were observed. During the infusion period, 85% of maximal inhibition was seen with 0.5 mg/kg, and this was increased to complete (100%) inhibition at 1.0 and 2.0 mg/kg. In addition to this increased effect during the infusion period, the duration of P-gp blockade was also increased. A dose of 2.0 mg/kg gave complete inhibition for in-excess-of 24 h. The 1-mg/kg cohort did not include a placebo, so it cannot be corrected for drift of the baseline. However, given the level of inhibition seen at the earliest time points, and from trends seen throughout this and other studies, it can be inferred that this dose level also gave close to full inhibition for 24 h.

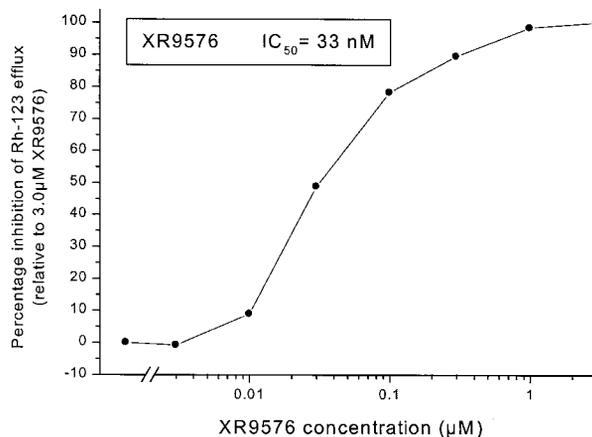


Fig. 3 Inhibition of P-gp in CD56⁺ cells by XR9576 added *ex vivo*. XR9576 was added at the indicated final concentrations to samples of blood from healthy volunteers. The blood was then analyzed for P-gp activity as detailed in “Materials and Methods.” The data presented are the mean of duplicate points and are representative of experiments carried out more than three times using blood from different volunteers.

Fig. 4 Surrogate marker activity after XR9576 0.1 mg/kg i.v. infusion. The accumulation of Rh-123 in CD56⁺ lymphocytes prepared from subjects during the above trial was measured as detailed in "Materials and Methods." Data are expressed as the percentage inhibition of individual subjects relative to the XR9576 spike. XR9576-dependent inhibition of P-gp is evident in subjects 2–4. Subject 1 received a placebo.

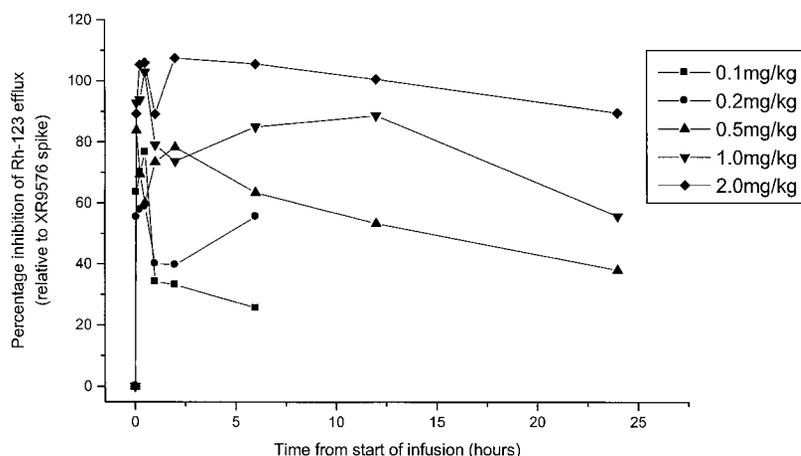
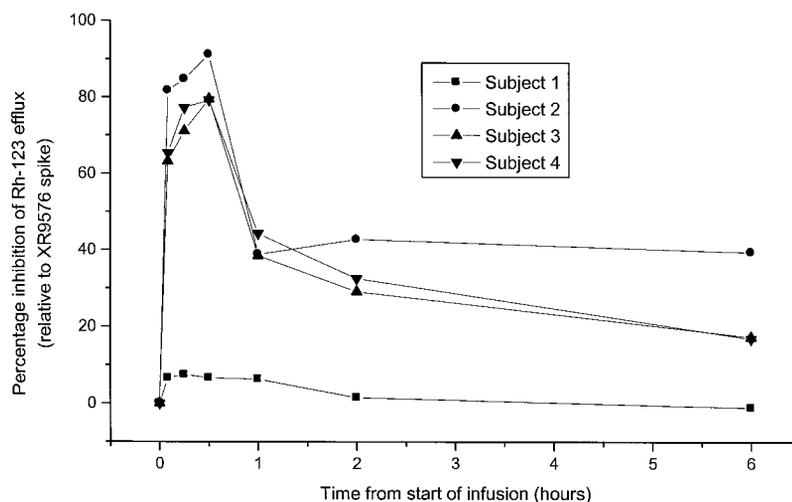


Fig. 5 Surrogate marker activity after infusion of escalating doses of XR9576. The accumulation of Rh-123 in CD56⁺ lymphocytes was measured as detailed in "Materials and Methods." The data shown represents the mean percentage inhibition of those subjects who were given XR9576 at the doses indicated.

A clear dose relationship was seen when data were compared at a single fixed time point (6 h). P-gp inhibition increased with the XR9576 dose until an asymptote was reached between 1.0 and 2.0 mg/kg (Fig. 6). The inhibition of P-gp at individual time points in individual subjects was also seen to correlate with XR9576 plasma concentrations measured in the same samples (Fig. 7) up to a plasma concentration of ~150–200 ng/ml that gave 100% blockade.

Inhibition of P-gp after Oral Administration of XR9576.

Inhibition of P-gp activity in CD56⁺ cells after oral administration of XR9576 was examined as described for the i.v. study. XR9576 was administered as a fixed dose in an oral capsule.

The lowest oral dose of XR9576 (50 mg) gave significant inhibition of P-gp activity in all four subjects who received the drug (Fig. 8). The level of inhibition varied between 40 and 80% (mean 65.6% ± 17.0) with a T_{max} between 2 and 6 h. Subject 30, who received XR9576 and had the lowest level of inhibition, also had substantially lower plasma levels of XR9576 than the other subjects (data not shown). Inhibition of P-gp slowly declined over time, but at 24 h, a mean of approximately 20% inhibition was still

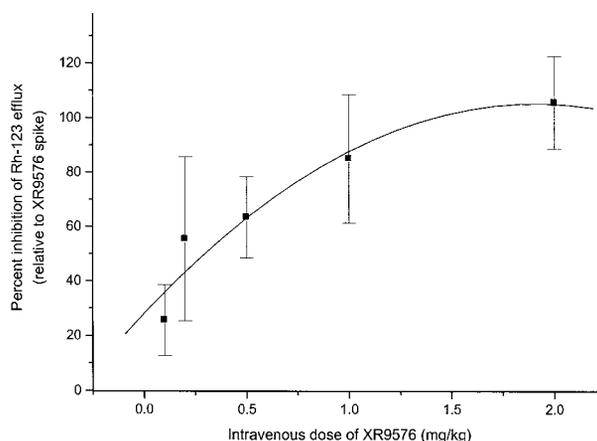


Fig. 6 Correlation between XR9576 i.v. dose and inhibition of P-gp in the surrogate marker assay. The accumulation of Rh-123 in CD56⁺ lymphocytes was measured as detailed in "Materials and Methods." Points represent the mean (± SD) percentage inhibition from all volunteers given XR9576 at each dose escalation.

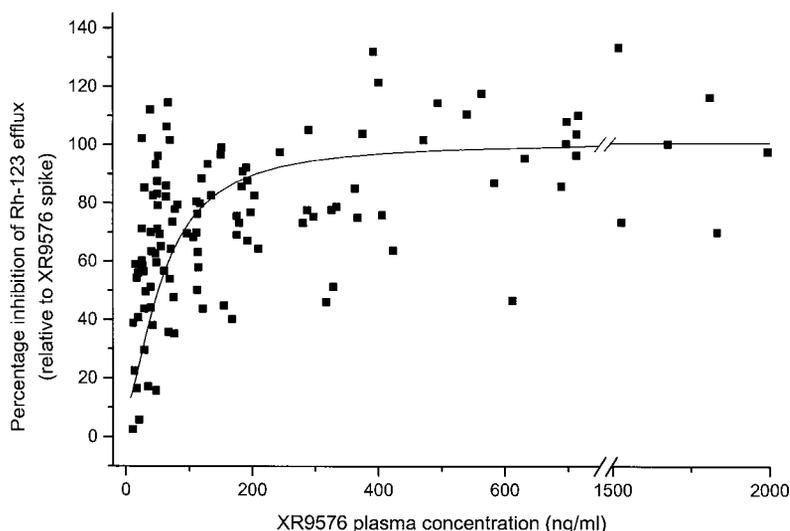
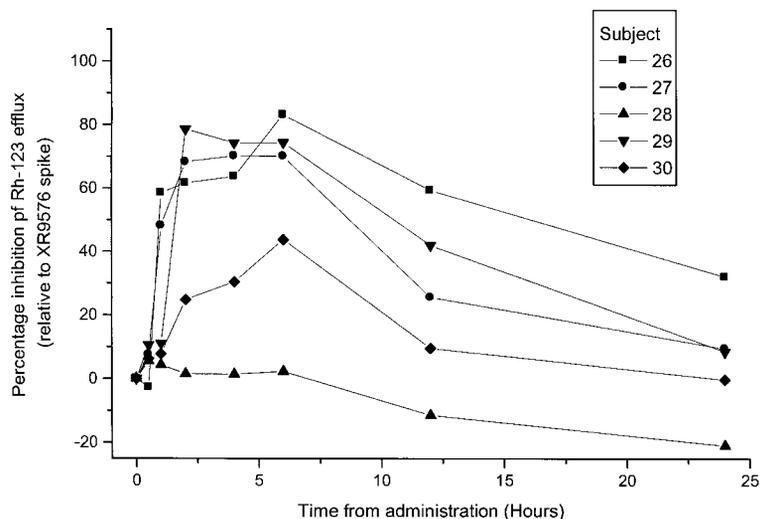


Fig. 7 Correlation between XR9576 plasma concentration and inhibition of P-gp in the surrogate marker assay. The plasma concentrations of XR9576 and accumulation of Rh-123 in CD56⁺ lymphocytes was measured as detailed in "Materials and Methods." Points represent the percentage inhibition from all volunteers given XR9576 at all dose levels plotted against the plasma concentration from the corresponding samples.

Fig. 8 Surrogate marker activity after oral administration of 50 mg of XR9576. The accumulation of Rh-123 in CD56⁺ lymphocytes was measured as detailed in "Materials and Methods." Data are expressed as the percentage inhibition for individual subjects. XR9576-dependent inhibition of P-gp is evident in subjects 26, 27, 29, and 30. Subject 28 received a placebo.



apparent. This value for inhibition of P-gp may be an underestimate, as the values obtained from the subject given a placebo (subject 28) showed a downward drift between 0 and 24 h. Normalization of the XR9576-treated group data to the placebo values would result in an increase in the apparent P-gp inhibition. Nevertheless, even in the absence of normalization of the data it is clear that XR9576 gave significant inhibition of P-gp after oral administration.

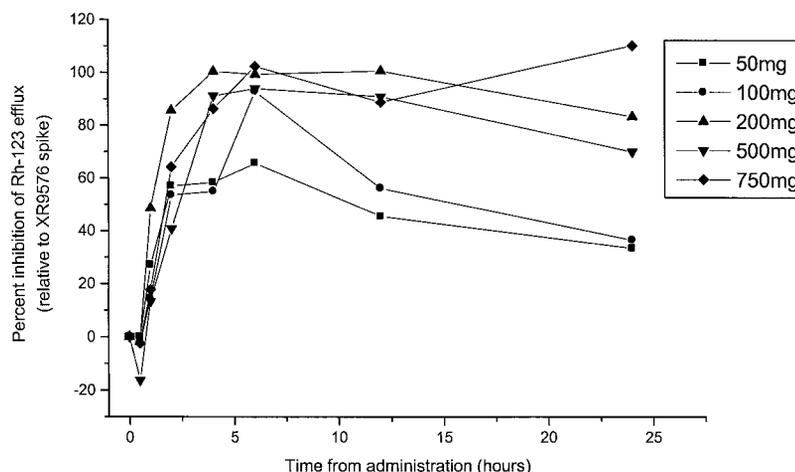
Higher oral doses of XR9576 resulted in maximal inhibition of P-gp and prolonged the duration of maximal activity (Fig. 9). Administration of 200, 500, and 750 mg all gave complete (100%) inhibition of P-gp activity in CD56⁺ cells between 4 and 12 h. The highest dose administered (750 mg) gave complete inhibition for in-excess-of 24 h, whereas 200 and 500 mg gave 80 and 70% inhibition at 24 h, respectively.

DISCUSSION

Although Phase I studies are primarily designed to assess the safety, tolerance and pharmacokinetics of a novel

drug, we chose to include a surrogate marker for XR9576 activity and to use this information to guide the selection of the XR9576 dose for Phase II studies. The CD56⁺/Rh-123 surrogate marker assay (11) has been used previously to show activity of the P-gp modulator, GG918 (12). This assay, which uses the relatively high expression of P-gp on CD56⁺ lymphocytes as a surrogate for multidrug resistant tumor cells, can be used to look at P-gp transport by flow cytometry in the presence or absence of a P-gp modulator. We have shown previously that XR9576 is a potent and specific P-gp modulator (8, 9), and this system uses the relatively high expression of P-gp on CD56⁺ lymphocytes. Thus we believe that the XR9576-mediated effect on Rh-123 accumulation reflects modulation of P-gp in this system. The data obtained in this Phase I trial are particularly encouraging when correlated with preclinical studies where XR9576 was seen to accumulate in tumors relative to plasma and where efficacy was observed in solid tumors (9). This correlation with preclinical data is important because one possible

Fig. 9 Surrogate marker activity after oral administration of escalating doses of XR9576. The accumulation of Rh-123 in CD56⁺ lymphocytes was measured as detailed in "Materials and Methods." The data shown represents the mean percentage inhibition of those subjects administered XR9576 at the doses indicated with the placebo values subtracted. Data from two 750-mg/kg data sets have been combined.



limitation of the surrogate marker assay is that P-gp modulation in a CD56⁺ lymphocytes may not address all of the issues associated with delivery of a drug to solid tumors.

Using this assay we have shown that an appropriate single dose of XR9576, administered by either the i.v. or the oral route, gives complete inhibition of P-gp for in excess of 24 h. Although the clinical trial design allowed for only one placebo control at each dose level, the data for these samples were consistent over the study and throughout the assay validation before initiation of the clinical trial (data not shown). These data demonstrate that XR9576 is a very effective modulator of P-gp in humans and support the excellent preclinical profile generated for this compound (8, 9).

The clear correlation between XR9576 plasma concentrations and inhibition of P-gp has allowed the definition of a target concentration of XR9576 for future studies where it may not be practical to run a surrogate marker assay. The results described here demonstrate that a XR9576 plasma concentration of approximately 150–200 ng/ml gave complete inhibition of P-gp. Plasma levels of XR9576 were in excess of the 200-ng/ml target concentration for in-excess-of 24 h (13), resulting in complete inhibition of P-gp throughout this period after i.v. (≥ 1.0 mg/kg) and oral administration (≥ 100 mg/volunteer). This suggests that XR9576 can be administered on a once-daily dosing regime and is supported by an elimination half-life of approximately 24 h.³ Importantly, XR9576 was well tolerated throughout these studies. No drug abnormalities were noted in any of the hematological or clinical chemistry parameters measured. These properties of XR9576 should allow simple incorporation into combination protocols with anticancer agents.

In conclusion, these data confirm the potential of XR9576 in the treatment of multidrug resistant tumors using well-tolerated regimens. The data have also supported the choice of XR9576 dose (150 mg/volunteer i.v. and 500 mg/volunteer p.o.) for Phase IIa clinical trials in a number of centers in the United States and the United Kingdom.

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³ Unpublished data.

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