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Research paper

# Towards repositioning of quinacrine for treatment of acute myeloid leukemia – Promising synergies and in vivo effects

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ABSTRACT

We previously reported that the anti-malarial drug quinacrine has potential to be repositioned for treatment of acute myeloid leukemia (AML). As a next step towards clinical use, we assessed the efficacy of quinacrine in an AML-PS mouse model and investigated possible synergistic effects when combining quinacrine with nine other antileukemic compounds in two AML cell lines. Furthermore, we explored the in vivo activity of quinacrine in combination with the widely used AML agent cytarabine.

The in vivo use of quinacrine (100 mg/kg three times per week for two consecutive weeks) significantly suppressed circulating blast cells at days 30/31 and increased the median survival time (MST). The in vitro drug combination analysis yielded promising synergistic interactions when combining quinacrine with cytarabine, azacitidine and geldanamycin. Finally, combining quinacrine with cytarabine in vivo showed a significant decrease in circulating leukemic blast cells and increased MST compared to the effect of either drug used alone, thus supporting the findings from the in vitro combination experiments.

Taken together, the repositioning potential of quinacrine for treatment of AML is reinforced by demonstrating significant in vivo activity and promising synergies when quinacrine is combined with different agents, including cytarabine, the hypomethylating agent azacitidine and HSP-90 inhibitor geldanamycin.

## 1. Introduction

Despite the recent advances in understanding the pathophysiology of acute myeloid leukemia (AML), the prognosis remains fatal for the majority of patients [1]. As of today, conventional AML treatment range from intensive chemotherapy, sometimes followed by hematopoietic stem cell transplantation, to hypomethylating agents or palliative treatment strategies. New treatment options and modalities are highly warranted.

We have previously reported in vitro results indicating that quinacrine, formerly extensively used as an antimalarial drug and later for treatment of Giardia Lamblia infections, may have repositioning potential for treatment in AML [2]. Quinacrine is an inexpensive oral compound with a well-documented safety profile, thereby making it attractive for repurposing in cancer treatment. Side effects of high-dose quinacrine have been reported to be tolerable and rare serious adverse effects like psychosis and aplastic anemia are all reversible upon cessation of therapy. Indeed, quinacrine has increasingly attracted interest as an anticancer agent with reported preclinical efficacy in a wide variety of malignancies such as breast cancer, glioma, colorectal and other gastrointestinal cancers [3–7]. Several preclinical studies report synergistic anticancer effect when quinacrine is combined with other agents, for instance erlotinib in non-small cell lung cancer (NSCLC) [8], paclitaxel in prostate cancer [9] as well as with cisplatin in 4 different cancer cell lines [10]. A recent study from Abdulghani et al. report additive/synergistic effects in vitro when quinacrine was combined with the kinase inhibitor sorafenib in anaplastic thyroid carcinoma models. This drug combination improved survival in an in vivo mouse model and triggered inhibition of NFκB as well as Mcl-1 [11]. A clinicaltrials.gov search (June 2017) reports ongoing or completed clinical trials regarding quinacrine in stage IIIB-IV NSCLC (combination with erlotinib, NCT01839955), advanced stage colorectal adenocarcinoma (combination with capecitabine, NCT01844076) and in patients with androgen-independent prostate cancer (NCT00417274).

Quinacrine treatment influences a number of different mediators involved in cancer cell development and inflammation. Several modes of actions have been proposed, including DNA intercalation, p53 induction and inhibition of NFκB, phospholipase A2 and topoisomerase

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activity [3,12–14]. We previously identified RNA polymerase I (pol-I) as a potential quinacrine target, supported by the downregulation of pol-I genes upon quinacrine treatment in AML [2]. Studies in K562 leukemic cells indicate that quinacrine induce apoptosis with mitochondrial modifications, p38 MAPK-activation and ERK1/2 inactivation [15]. Hossain et al. reported that quinacrine (and other acridine derivates) act as epigenetic changers, inducing de-silencing of methylated cancer genes and complemented by reduced DNMT1-activity at activated gene promoters [16].

The aims of this study were to further evaluate the potential of quinacrine for a clinical trial in AML by evaluating its efficacy in vivo in a patient-derived xenograft (PDX) mouse model as well as investigate its possible synergistic effect with other antileukemic compounds either in clinical use or with mechanism of actions theoretically appealing for combinations with quinacrine.

## 2. Materials and methods

### 2.1. Reagents

In the combinatorial studies; cytotoxic activity of quinacrine in combination with one of 9 different drugs (daunorubicin, cytarabine, azacitidine, decitabine, sorafenib, geldanamycin, All-Trans Retinoic Acid (ATRA), vorinostat, and arsenic trioxide) was evaluated in AML cell lines using the fluorometric microculture cytotoxicity assay (FMCA). The antitumoral activity of quinacrine and the standard AML drug cytarabine was also further evaluated in vivo using the human AML-PS model. Quinacrine, azacitidine, decitabine, ATRA, vorinostat and arsenic trioxide were purchased from Sigma-Aldrich Co (Stockholm, Sweden), sorafenib and geldanamycin from LC Laboratories (Woburn, MA, USA) and daunorubicin and cytarabine were obtained from Selleckchem (Houston, TX, USA). The range of drug concentrations used in the combination studies is summarized in Table 1.

### 2.2. Cell culture

The AML cell lines HL-60 and MV4-11 (both purchased from the American Type Culture Collection; ATCC, Rockville, MD, USA) were used to evaluate the in vitro combinatorial effects of quinacrine with the other drugs. Cells were kept in Dulbecco's Modified Eagle's Medium supplemented with 10% heat-inactivated fetal calf serum, 2 mM glutamine and 100 U/ml penicillin (Sigma-Aldrich Co) and split twice weekly. Cell viability was assessed by Trypan blue exclusion test.

### 2.3. Fluorometric microculture cytotoxicity assay – FMCA

The FMCA, described in detail previously [17,18] was used to evaluate the cytotoxic activity of quinacrine alone or in combination with either of 9 different drugs. The method is based on the fluorescence generated when non-fluorescent fluorescein diacetate is converted to fluorescein by cells with intact plasma membranes. Using an acoustic dispensing Echo 550 instrument equipped with Labcyte robotics (Labcyte Inc., CA, USA), drugs were distributed into 384-well microtiter plates from a DMSO or sterile water stock solution depending on solubility. The compounds were transferred to the plates in duplicate wells as threefold serial dilution with concentrations ranging from 8 μM to 0.0039 μM depending on the compound and cell line used (for details, see Table 1).

**Table 1**
Range of drug concentrations (μM) used in cell lines HL-60 and MV4-11 in the in vitro combination study.

| Drug | Range of drug concentrations (μM) | |
|---|---|---|
| | HL-60 | MV4-11 |
| Quinacrine | 0.75–3 | 0.75–3 |
| Daunorubicin | 0.0156–0.0625 | 0.0078–0.0312 |
| Cytarabine | 0.125–0.5 | 0.125–0.5 |
| Azacitidine | 2–8 | 0.5–2 |
| Decitabine | 2–8 | 2–8 |
| Sorafenib | 1–4 | 0.00391–0.0156 |
| Geldanamycin | 0.0625–0.25 | 0.0313–0.125 |
| All-Trans Retinoic Acid | 2–8 | 0.25–1 |
| Vorinostat | 0.5–2 | 0.5–2 |
| Arsenic Trioxide | 2–8 | 0.25–1 |

### 2.4. In vitro drug combination analysis

Assessment of combinatorial effects of all 9 different drug pairs, in both AML cell lines (HL-60 and MV4-11), was performed using conventional Bliss analysis, followed by null hypothesis significance testing, based on results from all 16 combinations of 4 different concentrations of each drug (including zero concentration). Synergistic drug combinations were pinpointed by developing a pipeline for statistical inference using resampling. This was in order to take into account the observed experimental variability in the duplicated in vitro experiments, performed at three different time points. Important background theory, details associated with the developed computational framework and information related to the interpretation of the results are thoroughly presented in Sections 1–8 of the Supplementary Material 1.

### 2.5. In vivo study of quinacrine alone and in combination with cytarabine

The activity of quinacrine in vivo was investigated in two different studies using the AML-PS model, where $5 \times 10^6$ AML-PS cells (originating from leukemic blast purified from the bone marrow of a 61-year-old man during the third leukemic relapse (M1)) were injected intravenously in female SCID mice (Charles River, Italy) [19]. The animals were maintained in cages using steam autoclaved bedding, γ-radiated diet and acidified mineral water. A uniquely numbered ear tag identified each animal. Mice were monitored daily for mortality and clinical signs and body weights were evaluated twice a week. Mice of the main groups were euthanized when signs of distress appeared: e.g. body weight loss, paralysis, dyspnea, ruffled fur or hunched posture. Gross examination was performed on all animals at sacrifice. Experimental procedures and methods were performed by Accelera (Serviano, Italy) in accordance with guidelines and with permissions from the local ethics committee (Nerviano Medical Sciences (NMS) Ethic Committee), study director was Marina Ciomei. All experimental protocols were approved by the NMS Ethics Committee.

In the first study, groups of ten mice were randomized to treatment with quinacrine or vehicle control after two days. Quinacrine was administered by oral gavage (po) at the dose of 100 mg/kg three times a week for two consecutive weeks; control animals were treated with vehicle (sucrose solution) intravenously (iv) only (twice a week for two weeks). Patient derived AML-PS tumor cells express HLA-A, B, C surface receptors of major histocompatibility complex. Previous characterization studies of the mouse model demonstrated the presence of circulating tumor cells starting from three – four weeks after injection. Blood aliquots were collected on days 30 and 31 to determine the percentage of circulating leukemic cells by FACS analysis. BD Cellquest software was used for data collection and analysis. A "lyse and wash" direct immunofluorescence staining method of the surface marker was applied. Briefly, 100 μL of blood was incubated with mouse anti-human HLA-A, B, C–FITC conjugated (clone G46-2.6, BD-Biosciences, San Josè, CA, USA) in the dark for 30 min at + 4 °C. To lyse red cells, 2 mL of Pharmlyse lysing buffer solution (BD-Biosciences) was added to the sample and incubated 15 min at room temperature in the dark. Cells were then collected by centrifugation and washed with staining buffer (PBS 1% Bovine Serum Albumin − Sigma, St. Louis, USA). The stained

samples were kept refrigerated and protected from light until collection to the cytometer (FACSCalibur −BD Biosciences, New Jersey, USA); at least 20,000 events from the WBC gate on FSC/SSC were acquired. Median survival time (MST) for each group was determined and log-rank test (Mantel-Cox) was used to evaluate statistical significance of differences between the control group vs. the quinacrine-treated group using GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA).

In the second study, groups of ten mice were randomized after 3 days into either of 5 treatment groups: 1) vehicle (glucose solution) iv only, 2) cytarabine intraperitoneally (ip) for two cycles of 5 consecutive days at the dose of 75 mg/kg, 3) quinacrine po at 100 mg/kg 3 times a week for 2 weeks, 4) quinacrine po at 100 mg/kg 3 times a week for 4 weeks, 5) combination of cytarabine ip for two cycles of 5 consecutive days at the dose of 75 mg/kg and simultaneously administered quinacrine po at 100 mg/kg 3 times a week for the same 2 weeks as the cytarabine treatment. MST was then determined for each group and a treatment to control ratio (T/C value (%)) was reported: $T/C = (MST_{compoundtreatedmice}/MST_{vehicletreatedmice}) \times 100$. Again, log-rank test (Mantel-Cox) was used to evaluate the statistical significance of differences between the different treatment groups.

## 3. Results

### 3.1. In vivo activity of quinacrine in a PDX model of AML

In the first AML mouse in vivo study, evaluation of circulating leukemic cells detected in blood samples (in percent of white blood cells (WBC)) at day 30/31 showed 72% human tumor cells in the control mice, whereas in mice treated with quinacrine, this was only 2.2% (Fig. 1a). In agreement with these data, the MST of control mice was 34 days whereas it was 46 days in quinacrine-treated mice ($p < 0.0001$, Fig. 1b). At the tested dose, quinacrine did not decrease the body weight of treated animals (Fig. 1 c).

### 3.2. In vitro drug combination analysis

In the in vitro drug combination analysis, several promising synergies were observed after studying repeated duplicate experiments, for instance when combining quinacrine with cytarabine, geldanamycin, ATRA, and the hypomethylating agent azacitidine. In Figs. 2 and 3, the statistically significant synergistic drug pairs detected for HL-60 and MV4-11 cell lines respectively, are presented in the form of heatmaps. More specifically, in the HL-60 cell line (Fig. 2), quinacrine in combination with four different drugs (cytarabine, azacitidine, geldanamycin, and ATRA) showed synergistic interactions. In the MV4-11 cell line (Fig. 3) quinacrine in combination with three different drugs (cytarabine, azacitidine and geldanamycin) appeared to be synergistic. The aforementioned results were detected at the 5% false alarm threshold using resampling. The Bliss index values for each combination concentration of all drug pairs and three replicates are included in Table 2, which is presented in the Supplementary Material.

### 3.3. In vivo activity of quinacrine in combination with cytarabine

Among the in vitro combination results demonstrating synergistic interactions with quinacrine, we selected cytarabine as the first combination partner to further investigate the in vivo activity in the PDX AML model. In this study, the circulating tumor cells were detected in blood samples on day 31 after tumor cell injection. In control mice, the percentage of human leukemic cells was 64.2%, in mice treated with cytarabine 2.3%, in those treated with quinacrine at 100 mg/kg for 2 weeks and 4 weeks 18.7% and 13.1% respectively, while the combination group showed only 0.2% circulating tumor cells (Fig. 4a).

The MST of control mice was 33 days whereas that of cytarabine-treated group was 48 days with a T/C value of 144%. Groups treated with quinacrine at 100 mg/kg showed a MST of 36 days (T/C: 109%)

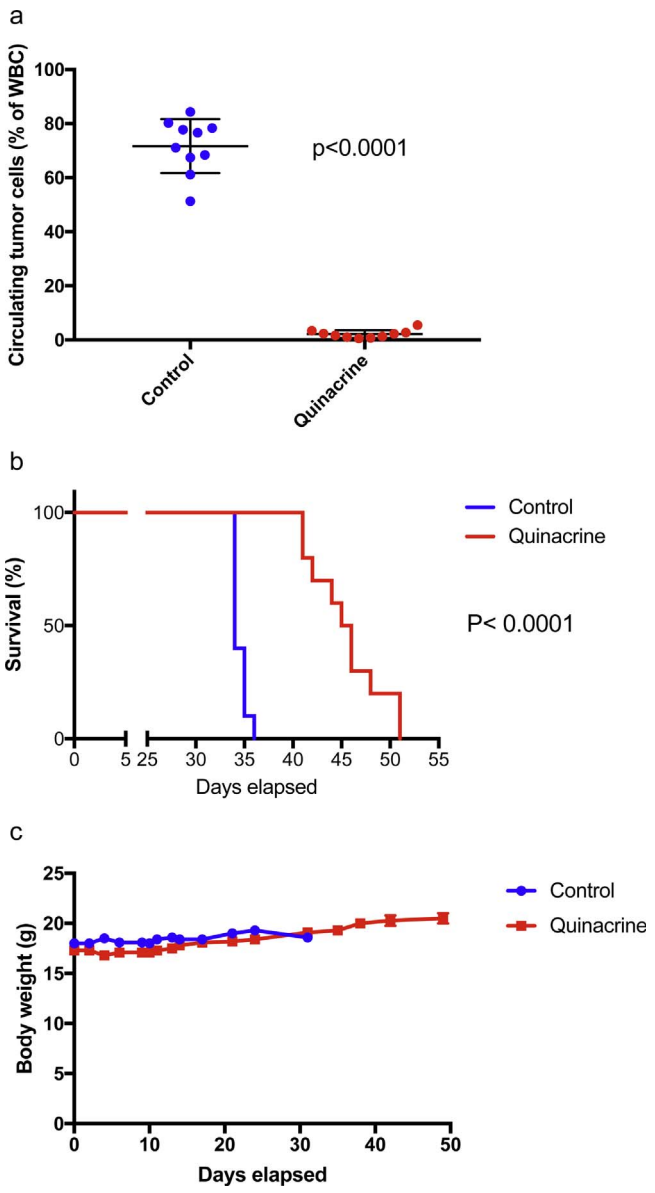


**Fig. 1.** In vivo effects of quinacrine (N = 10) and vehicle control (N = 10) in the first mouse study showing circulating tumor cells in blood on day 30 and 31 (in% of white blood cells (WBC)) (a), survival (b) and mean body weight (c.).

when the treatment continued for 2 weeks, and of 43 days (T/C: 130%), when the treatment was continued for 4 weeks. An additive effect was observed when cytarabine was combined with quinacrine, displaying a MST of 57 days with a T/C value of 171% (Fig. 4b). Log-rank test was used to determine differences between control group and all treated groups, all differences were statistically significant with $p = 0.0009$ for the group treated with 100 mg/kg quinacrine for 2 consecutive weeks and $p < 0.0001$ for all other groups. Results from the combination treatment were compared to those from single treatment with the two compounds and statistically significant results were obtained in both cases ($p = 0.003$ for combination vs. single cytarabine and $p < 0.0001$ for combination vs. single quinacrine 100 mg/kg for 2 weeks). At the tested doses, quinacrine did not decrease the body weight of treated mice but the combination resulted in a 12% drop in weight after the first cycle and 11% after the second, indicating some increased toxicity (Fig. 4c). For this reason, treatments of both compounds were stopped for 4 days after the first cycle.

All animals analyzed at gross autopsy showed splenomegaly and hepatomegaly. In some mice, enlarged thymus, solid tumor in ovary

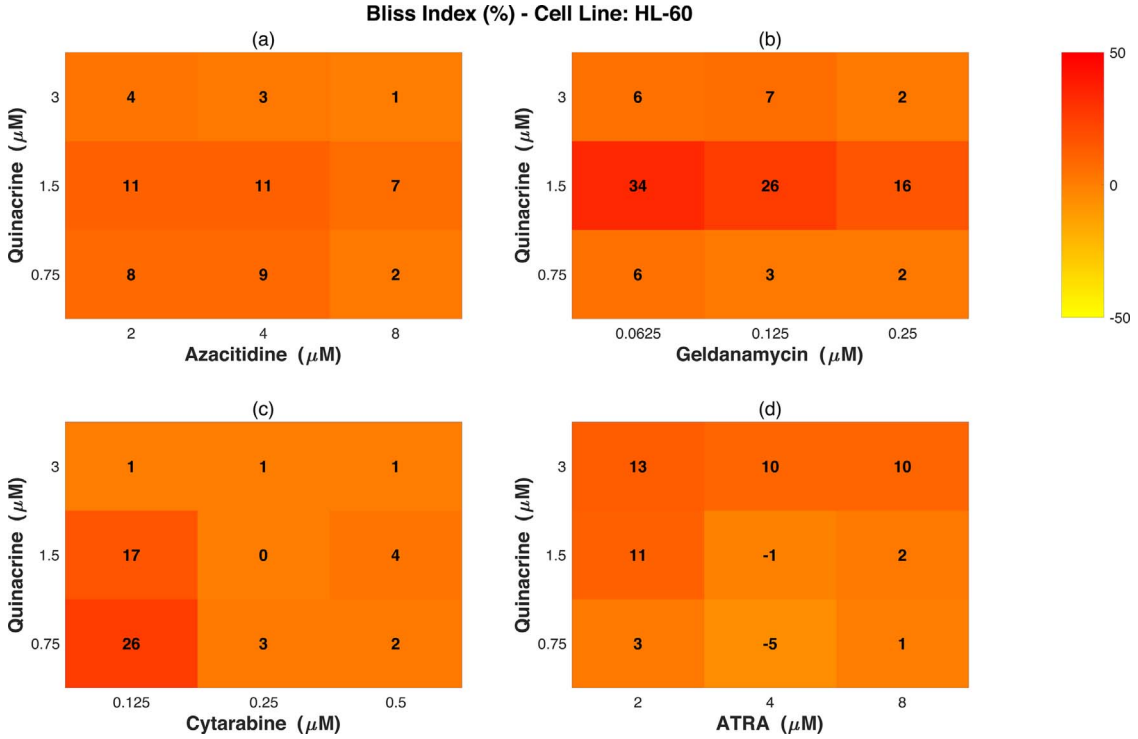


**Fig. 2.** Results of Bliss synergy analysis for the AML cell line HL-60, after simulating experimental data under the null hypothesis of Bliss independence and performing resampling. As shown, quinacrine in combination with four different drugs; azacitidine, geldanamycin, cytarabine and ATRA appear to be synergistic. Each drug pair is depicted by a 3 × 3 heat map where the color bar scale spans from −50% (yellow) to 50% (red), illustrating the mean Bliss difference index values (%) for all possible non-zero concentration combinations among the three different dates. Bliss index values that are equal or greater than 50% appear as red indicating the highest level of synergy, whereas values that are equal or smaller than −50% appear as yellow showing the highest level of antagonism. These four synergistic drug combinations are statistically significant, since they have been detected at the false alarm level of 5%.

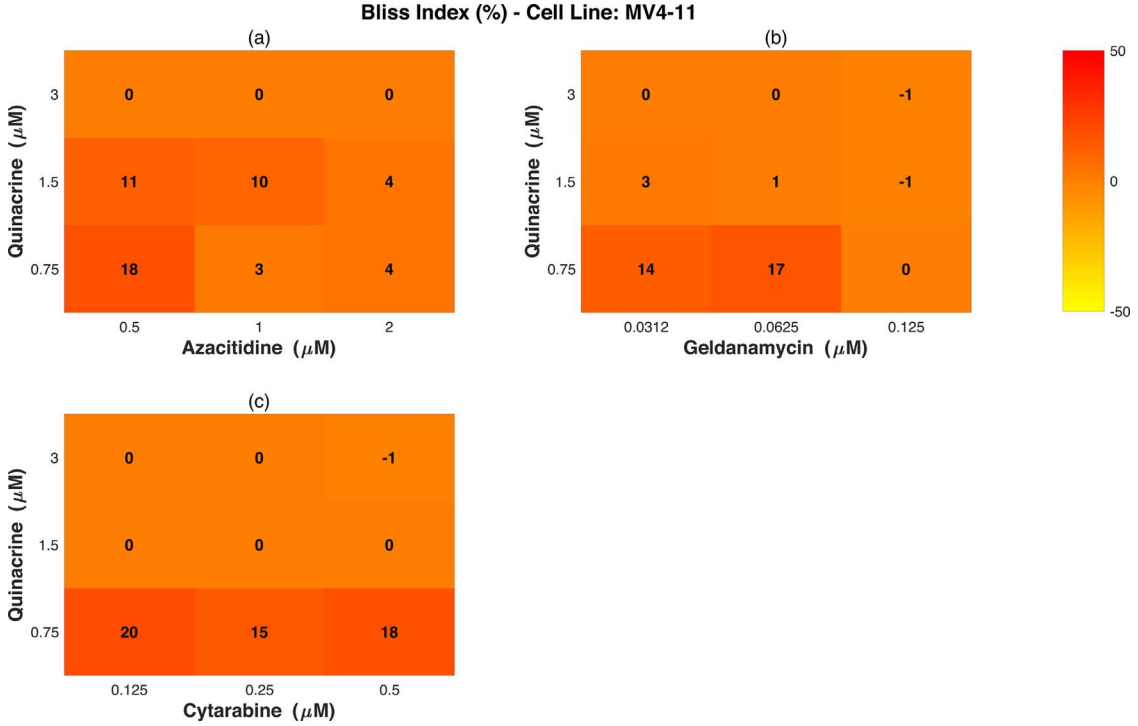


**Fig. 3.** Results of Bliss synergy analysis for the AML cell line MV4-11 after simulating experimental data under the null hypothesis of Bliss independence and performing resampling. As shown, quinacrine in combination with three different drugs; azacitidine, geldanamycin and cytarabine appear to be synergistic. Each drug pair is depicted by a 3 × 3 heat map where the color bar scale spans from −50% (yellow) to 50% (red), illustrating the mean Bliss difference index values (%) for all possible non-zero concentration combinations among the three different dates. Bliss index values that are equal or greater than 50% appear as red indicating the highest level of synergy, whereas values that are equal or smaller than −50% appear as yellow showing the highest level of antagonism. These three synergistic drug combinations are statistically significant, since they have been detected at the false alarm level of 5%.

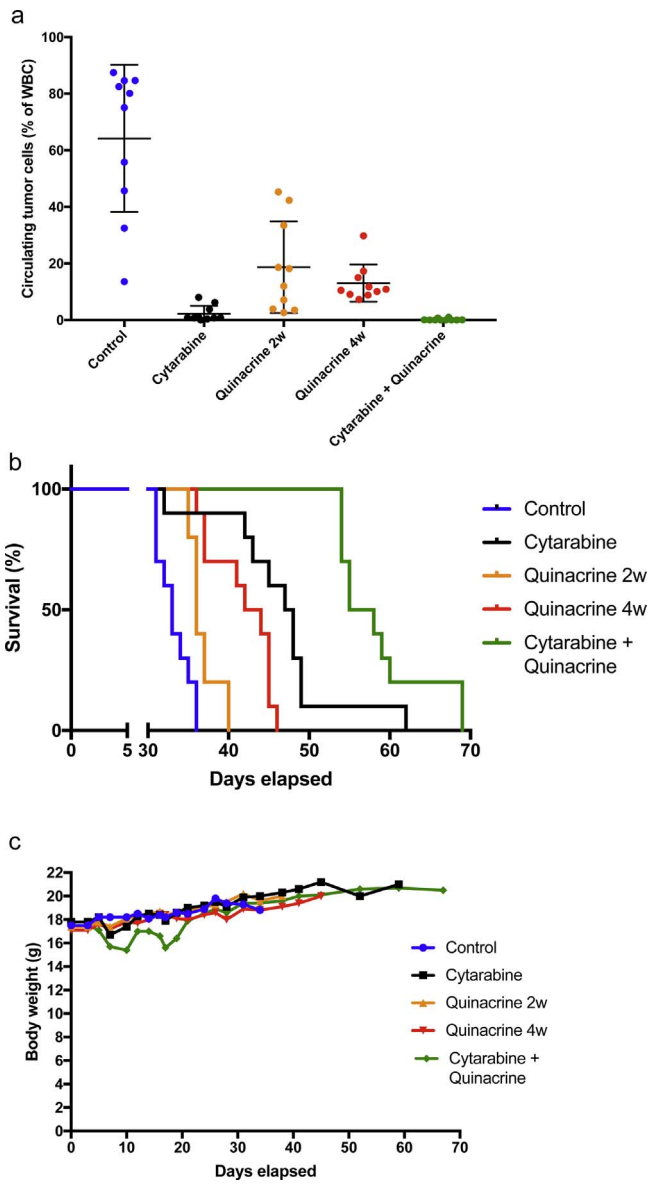


**Fig. 4.** In vivo effects of vehicle control, cytarabine, quinacrine administered for 2 weeks, quinacrine administered for 4 weeks and the simultaneous combination of quinacrine and cytarabine for 2 weeks (N = 10 animals/treatment group) in the second mouse study showing circulating tumor cells in blood on day 31 (in% of white blood cells (WBC)) (a) survival (b) and mean body weight (c).

and kidney were also observed. Solid tumors were observed in 1 animal in the cytarabine group and in 2 animals in the combination group. The reason for this is unclear but may be related to the longer survival time observed in these animals. A very high single dose of quinacrine (300 mg/kg) was also tested in an extra satellite group in this combination study. Although prolonging MST, solid tumors were observed also in this group and three out of 10 animals were sacrificed for toxicity reasons in including development of labyrinthitis (not shown).

## 4. Discussion and conclusion

In the present study, we demonstrate that quinacrine has in vivo efficacy in a PDX AML model, thus providing a basis for further clinical development in this disease. Quinacrine alone increased survival and reduced the number of circulating AML blasts in the absence of toxicity. A novel finding is also the clear synergistic effect between quinacrine and the standard AML drug cytarabine.

Quinacrine is rapidly taken up by the oral route and reaches plasma steady state concentration after 3–4 weeks with a half-life of 5–14 days [20]. Peak plasma concentrations of up to 0.32 μM for quinacrine have been reported for standard malaria regimens. The clinically used doses for *Giardia* treatment is 100 mg three times daily for 7 days, a dosing schedule that has also been found tolerable in long-term clinical studies of prion disease [21,22]. In this context, it is worth noting that the 100 mg/kg dose used in the animal study is close to the clinically achievable, also expressed as human equivalent surface area dose (approximately 500 mg for a 70 kg patient) [23]. Since there is an extensive cellular accumulation of 30–50 times that of plasma in white blood cells [22], a quinacrine dosing regimen of 300 mg three times daily is likely to reach clinically active intracellular concentrations.

In the present study, we also attempted to provide a possible clinical combination setting for quinacrine in AML by performing and analyzing in vitro combination experiments Among the 9 clinically used and experimental agents tested, cytarabine, azacitidine and geldanamycin showed promising synergistic effects when combined with quinacrine. In line with the in vitro findings, the combination of quinacrine and cytarabine resulted in improved anti-leukemic response and increased survival compared to the single drugs in the PDX model. Cytarabine is the backbone drug of AML treatment and it is used in multiple settings, including intensive induction chemotherapy, post-remission consolidation but also in low-dose regimens for older or frail patients who are ineligible for intensive therapy [24]. Cytarabine has been extensively studied in combination with other chemotherapeutics, as well as for single drug use in AML and the compound has been used repeatedly in the same patient with little evidence of cumulative toxicity [24–26]. However, before selecting the optimal combination partner for quinacrine in the clinical setting, more of the aforementioned promising in vitro combination pairs deserve to be tested in vivo and in particular, quinacrine along with the increasingly used hypomethylating drug azacitidine [27,28].

The mechanism(s) of action behind the synergistic effects of quinacrine and cytarabine, as shown both in vitro and vivo, remains unknown. In our previous study we demonstrated that quinacrine potentially could inhibit RNA polymerase-1 (pol-1) [2]. Pol-1 inhibitors have also shown promising preclinical activity in AML and one of these, CX-5461, is undergoing early clinical trials in cancer [29] (https://clinicaltrials.gov/ct2/show/NCT0271997). A consequence of rRNA inhibition is diminished transcription of anti-apoptotic genes. Therefore, the combination of pol-1 inhibitors and cytarabine may increase the sensitivity of AML cells to the cytotoxic effects of cytarabine by inhibiting the transcription of such genes. However, other mechanism described for quinacrine could also contribute to the positive interactions observed both in vitro and in vivo.

In the present study, geldanamycin produced synergistic interactions with quinacrine. Geldanamycin is a HSP-90 inhibitor and has been reported to synergize with different p53 activators to induce p53 mediated apoptosis [30]. Interestingly, it has been shown that upregulated rRNA synthesis dampens the p53 mediated response to cytotoxic stress which may at least partly explain a positive interaction between a pol-1 inhibitor and HSP-90 antagonists. [31]. The reported ability of pol-1 inhibitors to induce cancer cell-specific p53-mediated responses per se could be a major advantage for moving such agents into the clinic. Several HSP-90 inhibitors have been tested in clinical trials in the cancer area (e.g. ganetespib and AUY922) [32] and although not presently used in AML treatment, the potential synergies of pol-1 and HSP-90 inhibition make geldanamycin and other HSP-90 inhibitors highly interesting when designing combination studies for quinacrine.

In summary, our results strengthen the repositioning potential for quinacrine in AML treatment, suggesting in vivo efficacy as well as promising synergies with the standard AML drug cytarabine and the hypomethylating agent azacitidine. These results provide further support for evaluation of the anti-leukemic effect of quinacrine in a clinical

trial in AML.

## Author contributions

Conceived and designed the experiments: AE, EC, MF, JG, PN, MG, MH, RL. Performed the experiments: AE. Analyzed the data: AE, EC, MF, JG, PN, MG, MH, RL. Wrote the paper: AE, EC, MG, MH, RL.

## Potential conflict of interest

RL, PN and MF are co-founders and shareholders and MF CEO of Repos Pharma AB, a small Swedish research and development company dedicated to investigations of drug repositioning in the cancer area. The remaining authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2017.10.012.

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