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Original Paper

Lapatinib Induced Suicidal Death of Human Erythrocytes

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Key Words
Phosphatidylserine • Cell volume • Eryptosis • Calcium • Lapatinib

Abstract
Background/Aims: The human epidermal growth factor receptors tyrosine kinase inhibitor lapatinib has been shown to trigger suicidal death or apoptosis of tumor cells and is thus used for the treatment of malignancy. Side effects of lapatinib include anemia, which could, at least in theory, result from stimulation of eryptosis, the suicidal death of erythrocytes which is characterized by cell shrinkage and phospholipid scrambling of the cell membrane leading to phosphatidylserine translocation to the erythrocyte surface. Mechanisms involved in the triggering of eryptosis include oxidative stress, increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$), and ceramide. The present study explored, whether lapatinib induces eryptosis. ***Methods:*** Phosphatidylserine exposure at the cell surface was estimated from annexin-V-binding, cell volume from forward scatter, $[Ca^{2+}]_i$ from Fluo3-fluorescence, abundance of reactive oxygen species (ROS) from DCFDA dependent fluorescence, and ceramide abundance utilizing labelled specific antibodies. ***Results:*** A 48 hours exposure of human erythrocytes to lapatinib (≥ 1 µg/ml) significantly increased the percentage of annexin-V-binding cells, and significantly decreased forward scatter. Lapatinib (7.5 µg/ml) did not significantly modify DCFDA fluorescence and ceramide abundance. Lapatinib slightly, but significantly decreased Fluo3-fluorescence (≥ 5 µg/ml). Lapatinib (7.5 µg/ml) enhanced the annexin-V-binding in the presence of the Ca^{2+} ionophore ionomycin (1 µM) without significantly modifying Fluo3 fluorescence in the presence of ionomycin. The effect of lapatinib on forward scatter but not on annexin-V-binding was significantly blunted by removal of extracellular Ca^{2+}. ***Conclusion:*** Lapatinib triggers cell shrinkage and phospholipid scrambling of the erythrocyte cell membrane, an effect occurring despite decrease of cytosolic Ca^{2+} activity.

Introduction

Lapatinib, an inhibitor of human epidermal growth factor receptor (HER) tyrosine kinases [1-7], is utilized in the treatment of malignancy [1, 8-12], such as breast cancer [2-7, 13-45]. The drug is at least partially effective by triggering suicidal death or apoptosis

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of tumor cells [46-57]. On the other hand, lapatinib could counteract apoptosis induced by excessive glucose concentrations [58]. Side effects of lapatinib include skin rash, hand foot skin reaction and pruritus [8, 9, 11, 16, 23, 25, 26, 30, 59], alopecia [9, 23], leukopenia [9, 16, 25, 30], diarrhea, nausea and vomiting [9, 11, 16, 23, 25, 26, 30, 38, 59, 60], fatigue [11, 23, 30], peripheral neuropathy [9, 30], and anemia [9, 11, 25, 26, 61, 62].

The anemia could, at least in theory, result from eryptosis [63], the suicidal death of erythrocytes characterized by cell shrinkage [64] and phospholipid scrambling of the cell membrane with phosphatidylserine translocation to the cell surface [63]. Mechanisms stimulating eryptosis include increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$), oxidative stress [63], ceramide [65], energy depletion [63], caspases [63, 66, 67], casein kinase 1α, Janus-activated kinase JAK3, protein kinase C, and p38 kinase [63]. Eryptosis is inhibited by AMP activated kinase AMPK, cGMP-dependent protein kinase, sorafenib/sunitinib sensitive kinases, and PAK2 kinase [63] .

The present study explored whether lapatinib triggers eryptosis. To this end, human erythrocytes from healthy volunteers were treated with lapatinib and phosphatidylserine surface abundance, cell volume, $[Ca^{2+}]_i$, reactive oxygen species and ceramide abundance determined by flow cytometry.

Materials and Methods

Erythrocytes, solutions and chemicals

Fresh Li-Heparin-anticoagulated blood samples were kindly provided by the blood bank of the University of Tübingen. The study is approved by the ethics committee of the University of Tübingen (184/2003 V). The blood was centrifuged at 120 x g for 20 min at 21°C and the platelets and leukocytes-containing supernatant was disposed. Erythrocytes were incubated *in vitro* at a hematocrit of 0.4% in Ringer solution containing (in mM) 125 NaCl, 5 KCl, 1 $MgSO_4$, 32 N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES; pH 7.4), 5 glucose, 1 $CaCl_2$, at 37°C for 48 hours. Where indicated, erythrocytes were exposed to lapatinib (MedChem Express, Princeton, NJ, USA) at the indicated concentrations.

Annexin-V-binding and forward scatter

After incubation under the respective experimental condition, a 150 µl cell suspension was washed in Ringer solution containing 5 mM $CaCl_2$ and then stained with Annexin-V-FITC (1:200 dilution; ImmunoTools, Friesoythe, Germany) in this solution at 37°C for 20 min under protection from light. The annexin V abundance at the erythrocyte surface was subsequently determined on a FACS Calibur (BD, Heidelberg, Germany). Annexin-V-binding was measured with an excitation wavelength of 488 nm and an emission wavelength of 530 nm. A marker (M1) was placed to set an arbitrary threshold between annexin-V-binding cells and control cells. The same threshold was used for untreated and lapatinib treated erythrocytes. A dot plot of forward scatter (FSC) vs. side scatter (SSC) was set to linear scale for both parameters. The threshold of forward scatter was set at the default value of "52".

Intracellular Ca^{2+}

After incubation, erythrocytes were washed in Ringer solution and then loaded with Fluo-3/AM (Biotium, Hayward, USA) in Ringer solution containing 5 mM $CaCl_2$ and 5 µM Fluo-3/AM. The cells were incubated at 37°C for 30 min. Ca^{2+}-dependent fluorescence intensity was measured with an excitation wavelength of 488 nm and an emission wavelength of 530 nm on a FACS Calibur.

Reactive oxidant species (ROS)

Oxidative stress was determined utilizing 2',7'-dichlorodihydrofluorescein diacetate (DCFDA). After incubation, a 150 µl suspension of erythrocytes was washed in Ringer solution and then stained with DCFDA (Sigma, Schnelldorf, Germany) in Ringer solution containing DCFDA at a final concentration of 10 µM. Erythrocytes were incubated at 37°C for 30 min in the dark and then washed two times in Ringer solution. The DCFDA-loaded erythrocytes were resuspended in 200 µl Ringer solution, and ROS-dependent fluorescence intensity was measured at an excitation wavelength of 488 nm and an emission wavelength of 530 nm on a FACS Calibur (BD).

Ceramide abundance

To determine the ceramide abundance at the erythrocyte surface, a monoclonal antibody was used. After incubation, cells were stained for 1 h at 37°C with 1 µg/ml anti-ceramide antibody (clone MID 15B4; Alexis, Grünberg, Germany) in phosphate-buffered saline (PBS) containing 0.1% bovine serum albumin (BSA) at a dilution of 1:10. After two washing steps with PBS-BSA, cells were stained for 30 min with polyclonal fluorescein-isothiocyanate (FITC)-conjugated goat anti-mouse IgG and IgM specific antibody (BD Pharmingen, Hamburg, Germany) diluted 1:50 in PBS-BSA. Unbound secondary antibody was removed by repeated washing with PBS-BSA. Samples were then analyzed by flow cytometric analysis at an excitation wavelength of 488 nm and an emission wavelength of 530 nm.

Statistics

Data are expressed as arithmetic means ± SEM. As indicated in the figure legends, statistical analysis was made using ANOVA with Tukey's test as post-test and *t* test as appropriate. n denotes the number of different erythrocyte specimens studied. Since different erythrocyte specimens used in distinct experiments are differently susceptible to triggers of eryptosis, the same erythrocyte specimens have been used for control and experimental conditions.

Results

The present study explored, whether lapatinib stimulates suicidal erythrocyte death or eryptosis, which is characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine translocation to the cell surface. Phosphatidylserine exposing erythrocytes were identified utilizing annexin-V-binding, as determined by flow cytometry. The erythrocytes were analysed following incubation for 48 hours in Ringer solution without or with lapatinib (1 - 7.5 µg/ml). As shown in Fig. 1, a 48 hours exposure to lapatinib increased the percentage of phosphatidylserine exposing erythrocytes, an effect reaching statistical significance at 1 µg/ml lapatinib.

The second hallmark of eryptosis is cell shrinkage. In order to estimate erythrocyte volume, forward scatter was determined utilizing flow cytometry following a 48 hours incubation in Ringer solution without or with lapatinib (1 – 7.5 µg/ml). As illustrated in Fig. 2, lapatinib decreased erythrocyte forward scatter, an effect reaching statistical significance at 1 µg/ml lapatinib concentration. Fluo3 fluorescence was taken as measure of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$). As shown in Fig. 3, a 48 hours exposure to lapatinib slightly decreased the Fluo3 fluorescence, an effect reaching statistical significance at 5 µg/ml lapatinib.

In order to test whether lapatinib interfered with the measurement of cytosolic Ca^{2+} activity, additional experiments were performed in the absence and presence of the Ca^{2+} ionophore ionomycin (1 µM). As illustrated in Fig. 4, ionomycin increased the Fluo3 fluorescence to similarly high levels in the absence and presence of lapatinib (7.5 µg/ml). Despite the similar increase of $[Ca^{2+}]_i$ in the absence and presence of lapatinib, ionomycin increased annexin-V-binding to significantly higher levels in the presence than in the absence of 7.5 µg/ml lapatinib (Fig. 5). Ionomycin treatment was further followed by marked cell shrinkage, an effect slightly, but significantly blunted in the presence of 7.5 µg/ml lapatinib (Fig. 6).

A next series of experiments explored whether the lapatinib-induced translocation of phosphatidylserine or erythrocyte shrinkage required entry of extracellular Ca^{2+}. To this end, erythrocytes were incubated for 48 hours in the absence or presence of 7.5 µg/ml lapatinib in the presence or nominal absence of extracellular Ca^{2+}. As illustrated in Fig. 7, removal of extracellular Ca^{2+} did not significantly modify the effect of lapatinib on annexin-V-binding and even in the absence of extracellular Ca^{2+}, lapatinib significantly increased the percentage of annexin-V-binding erythrocytes. Thus, lapatinib-induced cell membrane scrambling did not depend on entry of extracellular Ca^{2+}. Removal of extracellular Ca^{2+} significantly blunted the effect of lapatinib on forward scatter (Fig. 8). However, even in the absence of extracellular Ca^{2+}, lapatinib significantly decreased the erythrocyte forward scatter. Thus, lapatinib-induced cell shrinkage was in part sensitive to the presence of extracellular Ca^{2+}.

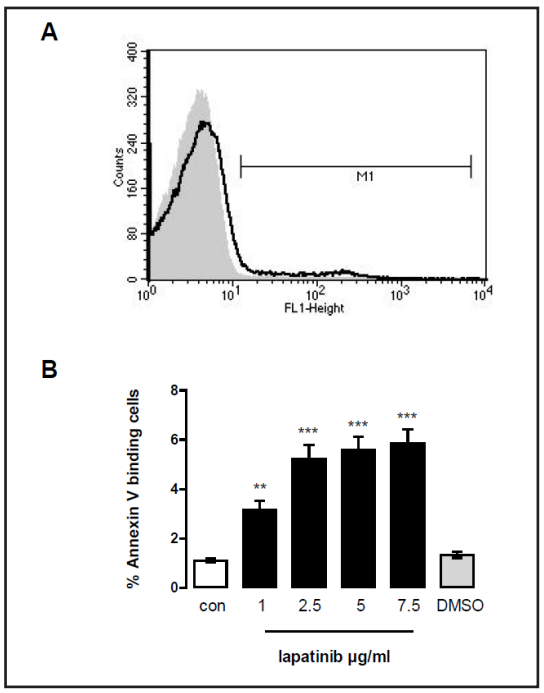

Fig. 1. Effect of lapatinib on phosphatidylserine exposure. (A) Original histogram of annexin-V-binding of erythrocytes following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of 7.5 µg/ml lapatinib. (B) Arithmetic means ± SEM (n = 20) of erythrocyte annexin-V-binding following incubation for 48 hours to Ringer solution without (white bar) or with (black bars) presence of lapatinib (1 - 7.5 µg/ml). For comparison, the effect of the solvent DMSO is shown (grey bar). **(p<0.01),***(p<0.001) indicates significant difference from the absence of lapatinib (ANOVA).

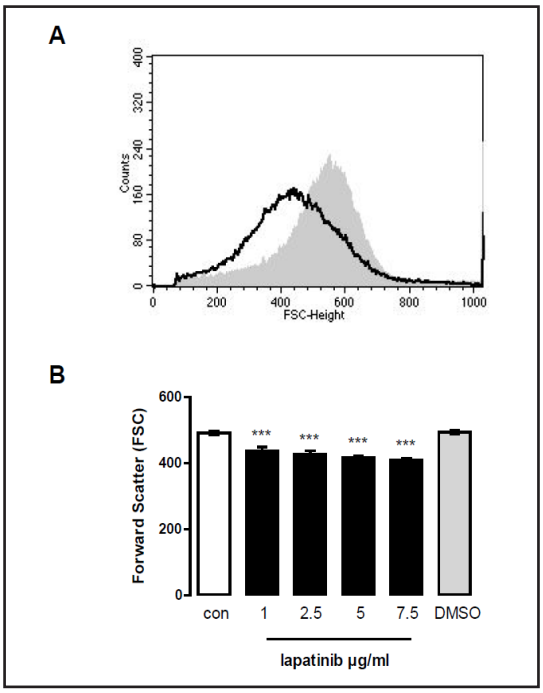

Fig. 2. Effect of lapatinib on erythrocyte forward scatter. (A) Original histogram of forward scatter of erythrocytes following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of 7.5 µg/ml lapatinib. (B) Arithmetic means ± SEM (n = 20) of the erythrocyte forward scatter (FSC) following incubation for 48 hours to Ringer solution without (white bar) or with (black bars) presence of lapatinib (1 - 7.5 µg/ml). For comparison, the effect of the solvent DMSO is shown (grey bar). ***(p<0.001) indicates significant difference from the absence of lapatinib (ANOVA).

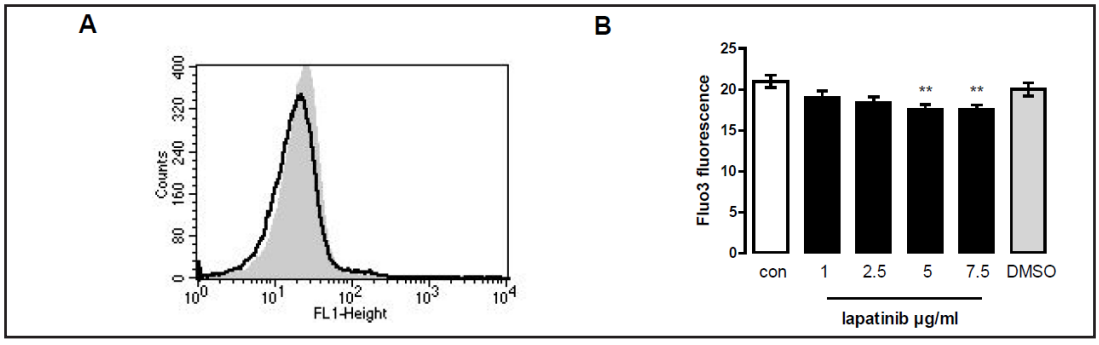

Fig. 3. Effect of lapatinib on erythrocyte Ca^{2+} activity. (A) Original histogram of Fluo3 fluorescence in erythrocytes following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of lapatinib (7.5 µg/ml). (B) Arithmetic means ± SEM (n = 17) of the Fluo3 fluorescence (arbitrary units) in erythrocytes exposed for 48 hours to Ringer solution without (white bar) or with (black bars) presence of lapatinib (1 – 7.5 µg/ml). For comparison, the effect of the solvent DMSO is shown (grey bar). **(p<0.01) indicates significant difference from the absence of lapatinib (ANOVA).

Reactive oxygen species (ROS) was quantified utilizing 2′,7′-dichlorodihydrofluorescein diacetate (DCFDA). A 48 hours exposure to lapatinib (7.5 µg/ml) did not significantly

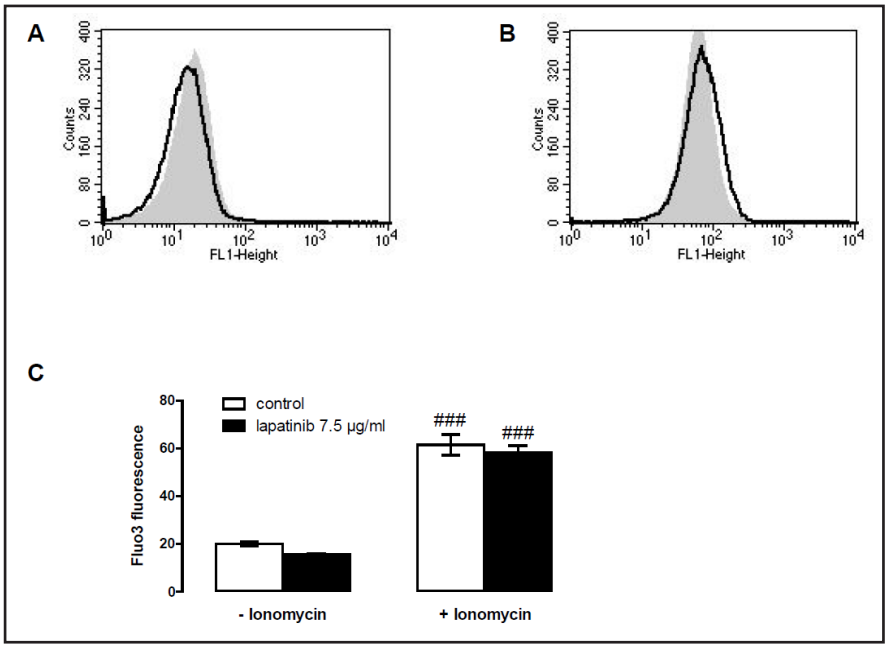

Fig. 4. Effect of the Ca^{2+} ionophore ionomycin on Fluo3 fluorescence in the absence and presence of lapatinib. (A, B) Original histogram of Fluo3 fluorescence in erythrocytes following exposure for 1 h to Ringer solution without (grey area) and with (black line) presence of lapatinib (7.5 µg/ml) in the absence (A) and presence (B) of ionomycin (1 µM). (C) Arithmetic means ± SEM (n = 10) of Fluo3 fluorescence in erythrocytes after a 1 h treatment with Ringer solution without (left bars) or with (right bars) ionomycin (1 µM) in the absence (white bars) and presence (black bars) of lapatinib (7.5 µg/ml). ###(p<0.001) indicates significant difference from the absence of ionomycin (ANOVA).

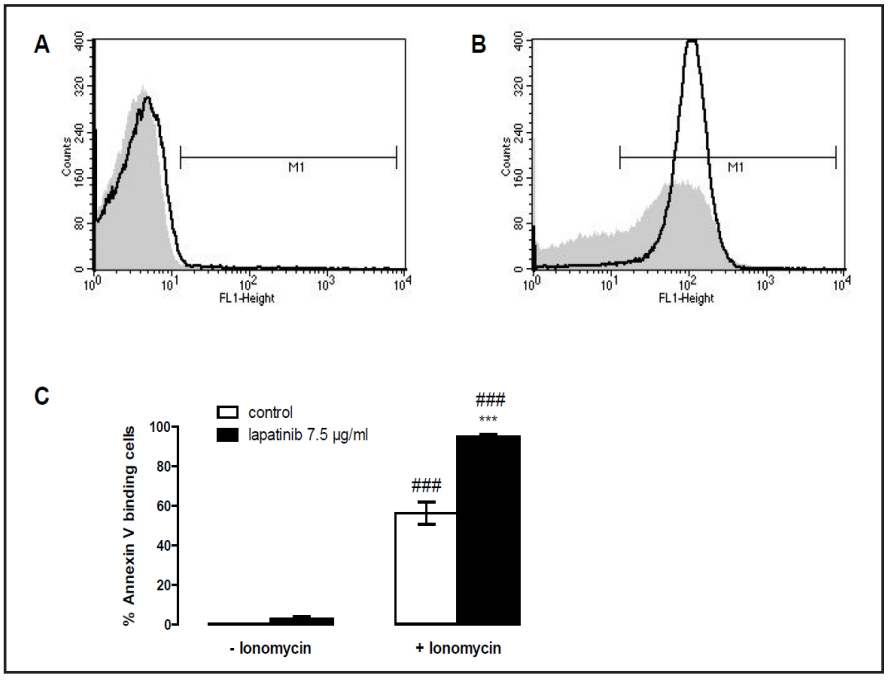

Fig. 5. Effect of the Ca^{2+} ionophore ionomycin on phosphatidylserine exposure in the absence and presence of lapatinib. (A, B) Original histogram of annexin-V-binding of erythrocytes following exposure for 1 h to Ringer solution without (grey area) and with (black line) presence of lapatinib (7.5 µg/ml) in the absence (A) and presence (B) of ionomycin (1 µM). (C) Arithmetic means ± SEM (n = 7) of annexin-V-binding of erythrocytes after a 1 h treatment with Ringer solution without (left bars) or with (right bars) ionomycin (1 µM) in the absence (white bars) and presence (black bars) of lapatinib (7.5 µg/ml). ***(p<0.001) indicates significant difference from the absence of lapatinib, ###(p<0.001) indicates significant difference from the absence of ionomycin (ANOVA).

increase the DCFDA fluorescence, which was similar in the presence (15.57 ± 0.38 a.u., n = 4) and in the absence (17.57 ± 0.99 a.u., n = 4) of lapatinib.

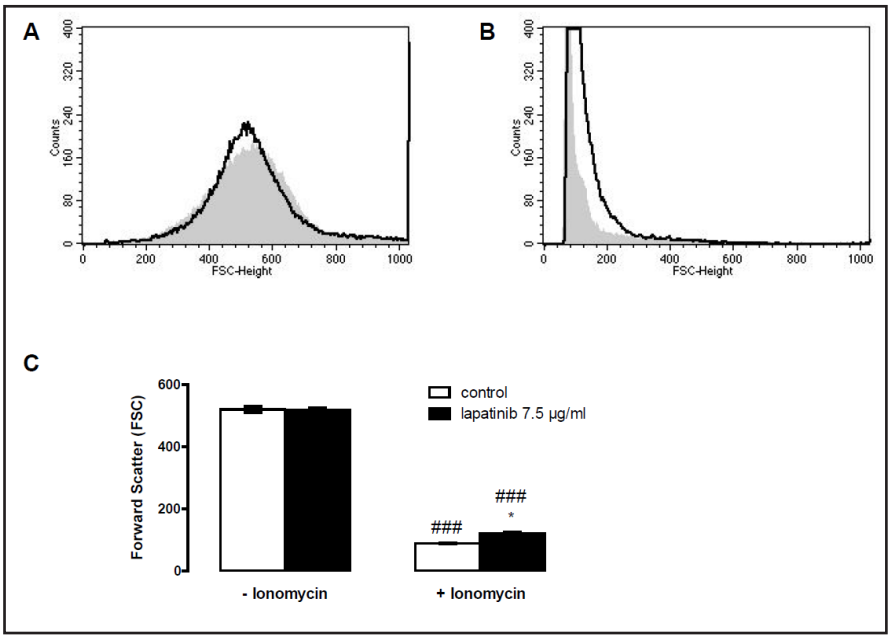

Fig. 6. Effect of the Ca^{2+} ionophore ionomycin on forward scatter in the absence and presence of lapatinib. (A, B) Original histogram of erythrocyte forward scatter following exposure for 1 h to Ringer solution without (grey area) and with (black line) presence of lapatinib (7.5 µg/ml) in the absence (A) and presence (B) of ionomycin (1 µM). (C) Arithmetic means ± SEM (n = 7) of erythrocyte forward scatter after a 1 h treatment with Ringer solution without (left bars) or with (right bars) ionomycin (1 µM) in the absence (white bars) and presence (black bars) of lapatinib (7.5 µg/ml). *(p<0.05) indicates significant difference from the absence of lapatinib, ###(p<0.001) indicates significant difference from the absence of ionomycin (ANOVA).

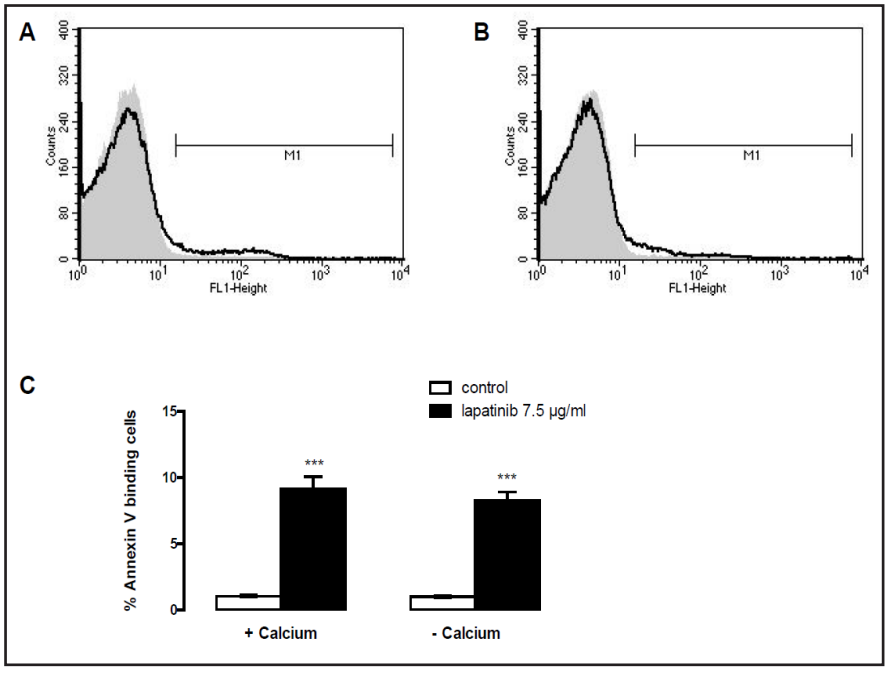

Fig. 7. Ca^{2+} sensitivity of lapatinib -induced phosphatidylserine exposure. (A, B) Original histogram of annexin-V-binding of erythrocytes following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of lapatinib (7.5 µg/ml) in the presence (A) and absence (B) of extracellular Ca^{2+}. (C) Arithmetic means ± SEM (n = 23) of annexin-V-binding of erythrocytes after a 48 hours treatment with Ringer solution without (white bars) or with (black bars) lapatinib (7.5 µg/ml) in the presence (left bars, $+Ca^{2+}$) and absence (right bars, $-Ca^{2+}$) of Ca^{2+}. ***(p<0.001) indicates significant difference from the absence of lapatinib (ANOVA).

Additional experiments addressed the impact of lapatinib on ceramide abundance at the erythrocyte surface. The ceramide abundance was quantified utilizing specific antibodies. As a result, following a 48 hours incubation, the ceramide abundance was similar following

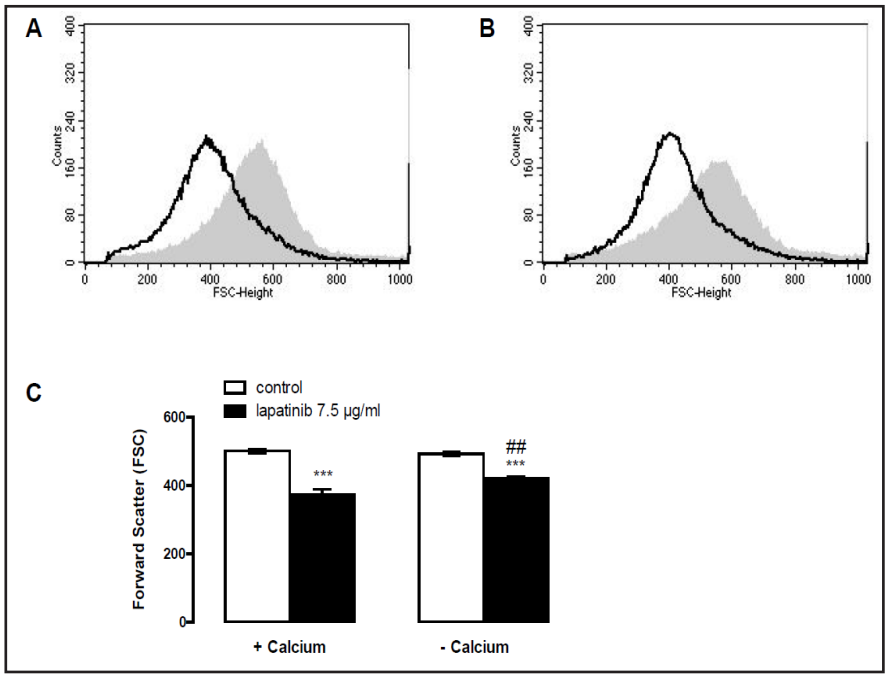

Fig. 8. Ca^{2+} sensitivity of lapatinib -induced erythrocyte shrinkage. (A, B) Original histogram of erythrocyte forward scatter following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of lapatinib (7.5 µg/ml) in the presence (A) and absence (B) of extracellular Ca^{2+}. (C) Arithmetic means ± SEM (n = 23) of erythrocyte forward scatter after a 48 hours treatment with Ringer solution without (white bars) or with (black bars) lapatinib (7.5 µg/ml) in the presence (left bars, $+Ca^{2+}$) and absence (right bars, $-Ca^{2+}$) of Ca^{2+}. ***($p<0.001$) indicates significant difference from the absence of lapatinib, ##($p<0.01$) indicates significant difference from the presence of Ca^{2+} (ANOVA).

incubation with 7.5 µg/ml lapatinib (13.9 ± 0.5 a.u., n = 4) and in the absence of lapatinib (14.2 ± 0.3 a.u., n = 4).

Discussion

The present observations reveal a novel effect of lapatinib, i.e. the triggering of suicidal erythrocyte death or eryptosis. Exposure of human erythrocytes to lapatinib results in cell shrinkage and cell membrane scrambling with phosphatidylserine translocation to the erythrocyte surface. The concentrations required for those effects are well in the range of lapatinib concentrations determined in patients [61]. Thus, the observed effect of lapatinib on eryptosis may well contribute to or even account for its effect on anemia, a major side effect of the drug [9, 11, 25, 26, 61, 62]. The sensitivity to lapatinib may be enhanced by clinical conditions known to enhance the susceptibility to triggers of eryptosis, such as dehydration [68], hyperphosphatemia [69], chronic kidney disease (CKD) [70-73], hemolytic-uremic syndrome [74], diabetes [75], hepatic failure [76], malignancy [63], sepsis [77], sickle-cell disease [63], beta-thalassemia [63], Hb-C and G6PD-deficiency [63], as well as Wilsons disease [78]. Moreover, eryptosis is stimulated by a wide variety of xenobiotics, which could, at least in theory, potentiate the effect of lapatinib on eryptosis [63, 68, 69, 71, 79-102].

Besides its effect on anemia [63], eryptosis fosters adherence of phosphatidylserine exposing erythrocytes to the vascular wall [103], stimulates blood clotting and triggers thrombosis [104-106]. Stimulation of eryptosis may thus impair microcirculation [65, 104, 107-110].

The effect of lapatinib on cell membrane scrambling and cell shrinkage was not due to increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$), which was actually decreased by lapatinib treatment. Moreover, the effect of lapatinib on cell membrane scrambling was insensitive to removal of extracellular Ca^{2+}. Instead, lapatinib augmented the effect of the Ca^{2+} ionophore ionomycin on cell membrane scrambling, an observation pointing to an effect of lapatinib downstream of $[Ca^{2+}]_i$.

Removal of extracellular Ca^{2+} slightly but significantly blunted the effect of lapatinib on erythrocyte shrinkage, which may partially depend on activity of Ca^{2+} sensitive K^+ channels accomplishing K^+ exit, cell membrane hyperpolarization, Cl^- exit and thus cellular loss of KCl with water [64]. Increase of $[Ca^{2+}]_i$ by the Ca^{2+} ionophore ionomycin was followed by the expected sharp decrease of forward scatter. The ionomycin induced cell shrinkage was slightly, but significantly blunted in the presence of lapatinib, an observation contrasting the shrinking effect of lapatinib in the absence of ionomycin. The present observations do not allow safe conclusions on the underlying mechanism. Possibly, lapatinib compromizes Na^+/K^+ ATPase activity, which would cause cellular K^+ loss, decrease cytosolic K^+ concentration and thus blunt the hyperpolarization following activation of Ca^{2+} sensitive K^+ channels.

The mechanism stimulating eryptosis following lapatinib treatment remains illdefined. According to DCFDA fluorescence, lapatinib treatment does not increase reactive oxygen species, a well known stimulator of eryptosis [63]. Moreover, Ca^{2+} entry is apparently not required for the stimulation of eryptosis by lapatinib. The effect of lapatinib is further not dependent on ceramide formation.

In conclusion, lapatinib triggers eryptosis with cell shrinkage and cell membrane scrambling, an effect not requiring increase of cytosolic Ca^{2+} activity.

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Disclosure Statement

The authors declare no conflict of interest.

References

1 Gandhi MD, Agulnik M: Targeted treatment of head and neck squamous-cell carcinoma: potential of lapatinib. Onco Targets Ther 2014;7:245-251.
2 Larsen PB, Kumler I, Nielsen DL: A systematic review of trastuzumab and lapatinib in the treatment of women with brain metastases from HER2-positive breast cancer. Cancer Treat Rev 2013;39:720-727.
3 Nolting M, Schneider-Merck T, Trepel M: Lapatinib. Recent Results Cancer Res 2014;201:125-143.
4 Rana P, Sridhar SS: Efficacy and tolerability of lapatinib in the management of breast cancer. Breast Cancer (Auckl) 2012;6:67-77.
5 Schneider-Merck T, Trepel M: Lapatinib. Recent Results Cancer Res 2010;184:45-59.
6 Tevaarwerk AJ, Kolesar JM: Lapatinib: a small-molecule inhibitor of epidermal growth factor receptor and human epidermal growth factor receptor-2 tyrosine kinases used in the treatment of breast cancer. Clin Ther 2009;31 Pt 2:2332-2348.
7 Wang H: Lapatinib for the treatment of breast cancer in the People's Republic of China. Onco Targets Ther 2014;7:1367-1373.
8 Abdel-Rahman O, Fouad M: Risk of mucocutaneous toxicities in patients with solid tumors treated with lapatinib: a systematic review and meta-analysis. Curr Med Res Opin 2015;31:975-986.
9 Chien AJ, Illi JA, Ko AH, Korn WM, Fong L, Chen LM, Kashani-Sabet M, Ryan CJ, Rosenberg JE, Dubey S, Small EJ, Jahan TM, Hylton NM, Yeh BM, Huang Y, Koch KM, Moasser MM: A phase I study of a 2-day lapatinib chemosensitization pulse preceding nanoparticle albumin-bound Paclitaxel for advanced solid malignancies. Clin Cancer Res 2009;15:5569-5575.

10 Harrington K, Berrier A, Robinson M, Remenar E, Housset M, de Mendoza FH, Fayette J, Mehanna H, El-Hariry I, Compton N, Franklin N, Biswas-Baldwin N, Lau M, Legenne P, Kumar R: Randomised Phase II study of oral lapatinib combined with chemoradiotherapy in patients with advanced squamous cell carcinoma of the head and neck: rationale for future randomised trials in human papilloma virus-negative disease. Eur J Cancer 2013;49:1609-1618.
11 Ramlau R, Thomas M, Novello S, Plummer R, Reck M, Kaneko T, Lau MR, Margetts J, Lunec J, Nutt J, Scagliotti GV: Phase I Study of Lapatinib and Pemetrexed in the Second-Line Treatment of Advanced or Metastatic Non-Small-Cell Lung Cancer With Assessment of Circulating Cell Free Thymidylate Synthase RNA as a Potential Biomarker. Clin Lung Cancer 2015;16:348-357.
12 Shimoyama S: Unraveling trastuzumab and lapatinib inefficiency in gastric cancer: Future steps (Review). Mol Clin Oncol 2014;2:175-181.
13 Ahn ER, Wang E, Gluck S: Is the Improved Efficacy of Trastuzumab and Lapatinib Combination Worth the Added Toxicity? A Discussion of Current Evidence, Recommendations, and Ethical Issues Regarding Dual HER2-Targeted Therapy. Breast Cancer (Auckl) 2012;6:191-207.
14 Amir E, Ocana A, Seruga B, Freedman O, Clemons M: Lapatinib and HER2 status: results of a meta-analysis of randomized phase III trials in metastatic breast cancer. Cancer Treat Rev 2010;36:410-415.
15 Bianchi GV, Duca M, Sica L, Mariani G: Metastatic breast cancer treated with lapatinib with a prolonged benefit: a case report and a review of therapeutic options available. Tumori 2013;99:269e-272e.
16 Botrel TE, Paladini L, Clark OA: Lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in the treatment of HER-2-overexpressing locally advanced or metastatic breast cancer: systematic review and meta-analysis. Core Evid 2013;8:69-78.
17 Bouchalova K, Cizkova M, Cwiertka K, Trojanec R, Friedecky D, Hajduch M: Lapatinib in breast cancer - the predictive significance of HER1 (EGFR), HER2, PTEN and PIK3CA genes and lapatinib plasma level assessment. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2010;154:281-288.
18 Brandes AA, Franceschi E, Tosoni A, Degli Esposti R: Trastuzumab and lapatinib beyond trastuzumab progression for metastatic breast cancer: strategies and pitfalls. Expert Rev Anticancer Ther 2010;10:179-184.
19 Cetin B, Benekli M, Dane F, Boruban C, Gumus M, Oksuzoglu B, Kaplan MA, Tufan G, Sevinc A, Coskun U, Buyukberber S: Lapatinib plus Capecitabine for HER2-Positive Advanced-Stage Breast Cancer in Elderly Women: Review of the Anatolian Society of Medical Oncology (ASMO) Experience. Breast Care (Basel) 2013;8:67-70.
20 Cetin B, Benekli M, Oksuzoglu B, Koral L, Ulas A, Dane F, Turker I, Kaplan MA, Koca D, Boruban C, Yilmaz B, Sevinc A, Berk V, Isikdogan A, Uncu D, Harputluoglu H, Coskun U, Buyukberber S: Lapatinib plus capecitabine for brain metastases in patients with human epidermal growth factor receptor 2-positive advanced breast cancer: a review of the Anatolian Society of Medical Oncology (ASMO) experience. Onkologie 2012;35:740-745.
21 Curran MP: Lapatinib: in postmenopausal women with hormone receptor-positive, HER2-positive metastatic breast cancer. Drugs 2010;70:1411-1422.
22 D'Amato V, Raimondo L, Formisano L, Giuliano M, De Placido S, Rosa R, Bianco R: Mechanisms of lapatinib resistance in HER2-driven breast cancer. Cancer Treat Rev 2015;10.1016/j.ctrv.2015.08.001
23 Esteva FJ, Franco SX, Hagan MK, Brewster AM, Somer RA, Williams W, Florance AM, Turner S, Stein S, Perez A: An open-label safety study of lapatinib plus trastuzumab plus paclitaxel in first-line HER2-positive metastatic breast cancer. Oncologist 2013;18:661-666.
24 Fleeman N, Bagust A, Boland A, Dickson R, Dundar Y, Moonan M, Oyee J, Blundell M, Davis H, Armstrong A, Thorp N: Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis. Health Technol Assess 2011;15:1-93, iii-iv.
25 Fumoleau P, Koch KM, Brain E, Lokiec F, Rezai K, Awada A, Hayward L, Werutsky G, Bogaerts J, Marreaud S, Cardoso F: A phase I pharmacokinetics study of lapatinib and tamoxifen in metastatic breast cancer (EORTC 10053 Lapatam study). Breast 2014;23:663-669.
26 Gajria D, Gonzalez J, Feigin K, Patil S, Chen C, Theodoulou M, Drullinsky P, D'Andrea G, Lake D, Norton L, Hudis CA, Traina TA: Phase II trial of a novel capecitabine dosing schedule in combination with lapatinib for the treatment of patients with HER2-positive metastatic breast cancer. Breast Cancer Res Treat 2012;131:111-116.

27 Giampaglia M, Chiuri VE, Tinelli A, De Laurentiis M, Silvestris N, Lorusso V: Lapatinib in breast cancer: clinical experiences and future perspectives. Cancer Treat Rev 2010;36 Suppl 3:S72-79.
28 Goss PE, Smith IE, O'Shaughnessy J, Ejlertsen B, Kaufmann M, Boyle F, Buzdar AU, Fumoleau P, Gradishar W, Martin M, Moy B, Piccart-Gebhart M, Pritchard KI, Lindquist D, Chavarri-Guerra Y, Aktan G, Rappold E, Williams LS, Finkelstein DM, investigators T: Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:88-96.
29 Hurvitz SA, Kakkar R: Role of lapatinib alone or in combination in the treatment of HER2-positive breast cancer. Breast Cancer (Dove Med Press) 2012;4:35-51.
30 Jagiello-Gruszfeld A, Tjulandin S, Dobrovolskaya N, Manikhas A, Pienkowski T, DeSilvio M, Ridderheim M, Abbey R: A single-arm phase II trial of first-line paclitaxel in combination with lapatinib in HER2-overexpressing metastatic breast cancer. Oncology 2010;79:129-135.
31 Jones J, Takeda A, Picot J, von Keyserlingk C, Clegg A: Lapatinib for the treatment of HER2-overexpressing breast cancer. Health Technol Assess 2009;13:S1-6.
32 Krop IE, Lin NU, Blackwell K, Guardino E, Huober J, Lu M, Miles D, Samant M, Welslau M, Dieras V: Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol 2015;26:113-119.
33 Krop IE, LoRusso P, Miller KD, Modi S, Yardley D, Rodriguez G, Guardino E, Lu M, Zheng M, Girish S, Amler L, Winer EP, Rugo HS: A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. J Clin Oncol 2012;30:3234-3241.
34 MacFarlane RJ, Gelmon KA: Lapatinib for breast cancer: a review of the current literature. Expert Opin Drug Saf 2011;10:109-121.
35 Mayer IA, Arteaga CL: Does lapatinib work against HER2-negative breast cancers? Clin Cancer Res 2010;16:1355-1357.
36 Merriam P, Sikov WM: Clinical utility of the combination of lapatinib and letrozole in the management of hormone receptor-positive and HER2-positive advanced breast cancer. Breast Cancer (Dove Med Press) 2011;3:139-150.
37 Moreira C, Kaklamani V: Lapatinib and breast cancer: current indications and outlook for the future. Expert Rev Anticancer Ther 2010;10:1171-1182.
38 Opdam FL, Guchelaar HJ, Beijnen JH, Schellens JH: Lapatinib for advanced or metastatic breast cancer. Oncologist 2012;17:536-542.
39 Riemsma R, Forbes CA, Amonkar MM, Lykopoulos K, Diaz JR, Kleijnen J, Rea DW: Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). Curr Med Res Opin 2012;28:1263-1279.
40 Riera R, Soarez PC, Puga ME, Ferraz MB: Lapatinib for treatment of advanced or metastasized breast cancer: systematic review. Sao Paulo Med J 2009;127:295-301.
41 Rolski J, Karczmarek-Borowska B, Smietana A: The possibility of lapatinib treatment for breast cancer patients with central nervous system metastases. Case study and literature review. Contemp Oncol (Pozn) 2012;16:582-585.
42 Steger GG, Abrahamova J, Bacanu F, Brincat S, Brize A, Cesas A, Cufer T, Dank M, Duchnowska R, Eniu A, Jassem J, Kahan Z, Matos E, Padrik P, Plate S, Pokker H, Purkalne G, Timcheva C, Tzekova V, Vyzula R, Zielinski CC: Current standards in the treatment of metastatic breast cancer with focus on Lapatinib: a review by a Central European Consensus Panel. Wien Klin Wochenschr 2010;122:368-379.
43 Vogel C, Chan A, Gril B, Kim SB, Kurebayashi J, Liu L, Lu YS, Moon H: Management of ErbB2-positive breast cancer: insights from preclinical and clinical studies with lapatinib. Jpn J Clin Oncol 2010;40:999-1013.
44 Vrdoljak E, Boban M, Ban M: Lapatinib in the treatment of HER-2 overexpressing breast cancer. J BUON 2011;16:393-399.
45 Yip AY, Tse LA, Ong EY, Chow LW: Survival benefits from lapatinib therapy in women with HER2-overexpressing breast cancer: a systematic review. Anticancer Drugs 2010;21:487-493.
46 Brady SW, Zhang J, Tsai MH, Yu D: PI3K-independent mTOR activation promotes lapatinib resistance and IAP expression that can be effectively reversed by mTOR and Hsp90 inhibition. Cancer Biol Ther 2015;16:402-411.

47 Chen S, Zhu X, Qiao H, Ye M, Lai X, Yu S, Ding L, Wen A, Zhang J: Protective autophagy promotes the resistance of HER2-positive breast cancer cells to lapatinib. Tumour Biol 2015;10.1007/s13277-015-3800-9
48 Huang W, Wu QD, Zhang M, Kong YL, Cao PR, Zheng W, Xu JH, Ye M: Novel Hsp90 inhibitor FW-04-806 displays potent antitumor effects in HER2-positive breast cancer cells as a single agent or in combination with lapatinib. Cancer Lett 2015;356:862-871.
49 Huo ZJ, Wang SJ, Wang ZQ, Zuo WS, Liu P, Pang B, Liu K: Novel nanosystem to enhance the antitumor activity of lapatinib in breast cancer treatment: Therapeutic efficacy evaluation. Cancer Sci 2015;10.1111/cas.12737
50 Kaczynska A, Swierczynska J, Herman-Antosiewicz A: Sensitization of HER2 Positive Breast Cancer Cells to Lapatinib Using Plants-Derived Isothiocyanates. Nutr Cancer 2015;67:976-986.
51 Karakashev SV, Reginato MJ: Hypoxia/HIF1alpha induces lapatinib resistance in ERBB2-positive breast cancer cells via regulation of DUSP2. Oncotarget 2015;6:1967-1980.
52 Lee J, Bartholomeusz C, Mansour O, Humphries J, Hortobagyi GN, Ordentlich P, Ueno NT: A class I histone deacetylase inhibitor, entinostat, enhances lapatinib efficacy in HER2-overexpressing breast cancer cells through FOXO3-mediated Bim1 expression. Breast Cancer Res Treat 2014;146:259-272.
53 Park SH, Ito K, Olcott W, Katsyv I, Halstead-Nussloch G, Irie HY: PTK6 inhibition promotes apoptosis of Lapatinib-resistant Her2(+) breast cancer cells by inducing Bim. Breast Cancer Res 2015;17:86.
54 Shiota M, Bishop JL, Takeuchi A, Nip KM, Cordonnier T, Beraldi E, Kuruma H, Gleave ME, Zoubeidi A: Inhibition of the HER2-YB1-AR axis with Lapatinib synergistically enhances Enzalutamide anti-tumor efficacy in castration resistant prostate cancer. Oncotarget 2015;6:9086-9098.
55 Wan X, Zheng X, Pang X, Zhang Z, Jing T, Xu W, Zhang Q: The potential use of lapatinib-loaded human serum albumin nanoparticles in the treatment of triple-negative breast cancer. Int J Pharm 2015;484:16-28.
56 Yan YY, Guo Y, Zhang W, Ma CG, Zhang YX, Wang C, Wang HX: Celastrol enhanced the anticancer effect of lapatinib in human hepatocellular carcinoma cells in vitro. J BUON 2014;19:412-418.
57 Zhang Z, Wang J, Ji D, Wang C, Liu R, Wu Z, Liu L, Zhu D, Chang J, Geng R, Xiong L, Fang Q, Li J: Functional genetic approach identifies MET, HER3, IGF1R, INSR pathways as determinants of lapatinib unresponsiveness in HER2-positive gastric cancer. Clin Cancer Res 2014;20:4559-4573.
58 Benter IF, Sarkhou F, Al-Khaldi AT, Chandrasekhar B, Attur S, Dhaunsi GS, Yousif MH, Akhtar S: The dual targeting of EGFR and ErbB2 with the inhibitor Lapatinib corrects high glucose-induced apoptosis and vascular dysfunction by opposing multiple diabetes-induced signaling changes. J Drug Target 2015;23:506-518.
59 Frankel C, Palmieri FM: Lapatinib side-effect management. Clin J Oncol Nurs 2010;14:223-233.
60 Bowen JM: Development of the rat model of lapatinib-induced diarrhoea. Scientifica (Cairo) 2014;2014:194185.
61 Inoue K, Kuroi K, Shimizu S, Rai Y, Aogi K, Masuda N, Nakayama T, Iwata H, Nishimura Y, Armour A, Sasaki Y: Safety, pharmacokinetics and efficacy findings in an open-label, single-arm study of weekly paclitaxel plus lapatinib as first-line therapy for Japanese women with HER2-positive metastatic breast cancer. Int J Clin Oncol 2015;10.1007/s10147-015-0832-5
62 Lorenzen S, Riera Knorrenschild J, Haag GM, Pohl M, Thuss-Patience P, Bassermann F, Helbig U, Weissinger F, Schnoy E, Becker K, Stocker G, Ruschoff J, Eisenmenger A, Karapanagiotou-Schenkel I, Lordick F: Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: a randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Eur J Cancer 2015;51:569-576.
63 Lang F, Qadri SM: Mechanisms and significance of eryptosis, the suicidal death of erythrocytes. Blood Purif 2012;33:125-130.
64 Lang PA, Kaiser S, Myssina S, Wieder T, Lang F, Huber SM: Role of Ca2+-activated K+ channels in human erythrocyte apoptosis. Am J Physiol Cell Physiol 2003;285:C1553-C1560.
65 Abed M, Towhid ST, Mia S, Pakladok T, Alesutan I, Borst O, Gawaz M, Gulbins E, Lang F: Sphingomyelinase-induced adhesion of eryptotic erythrocytes to endothelial cells. Am J Physiol Cell Physiol 2012;303:C991-999.
66 Lau IP, Chen H, Wang J, Ong HC, Leung KC, Ho HP, Kong SK: In vitro effect of CTAB- and PEG-coated gold nanorods on the induction of eryptosis/erythroptosis in human erythrocytes. Nanotoxicology 2012;6:847-856.

67 Maellaro E, Leoncini S, Moretti D, Del Bello B, Tanganelli I, De Felice C, Ciccoli L: Erythrocyte caspase-3 activation and oxidative imbalance in erythrocytes and in plasma of type 2 diabetic patients. Acta Diabetol 2013;50:489-495.
68 Abed M, Feger M, Alzoubi K, Pakladok T, Frauenfeld L, Geiger C, Towhid ST, Lang F: Sensitization of erythrocytes to suicidal erythrocyte death following water deprivation. Kidney Blood Press Res 2013;37:567-578.
69 Voelkl J, Alzoubi K, Mamar AK, Ahmed MS, Abed M, Lang F: Stimulation of suicidal erythrocyte death by increased extracellular phosphate concentrations. Kidney Blood Press Res 2013;38:42-51.
70 Abed M, Artunc F, Alzoubi K, Honisch S, Baumann D, Foller M, Lang F: Suicidal erythrocyte death in end-stage renal disease. J Mol Med (Berl) 2014;92:871-879.
71 Ahmed MS, Langer H, Abed M, Voelkl J, Lang F: The uremic toxin acrolein promotes suicidal erythrocyte death. Kidney Blood Press Res 2013;37:158-167.
72 Polak-Jonkisz D, Purzyc L: Ca(2+) influx versus efflux during eryptosis in uremic erythrocytes. Blood Purif 2012;34:209-210; author reply 210.
73 Calderon-Salinas JV, Munoz-Reyes EG, Guerrero-Romero JF, Rodriguez-Moran M, Bracho-Riquelme RL, Carrera-Gracia MA, Quintanar-Escorza MA: Eryptosis and oxidative damage in type 2 diabetic mellitus patients with chronic kidney disease. Mol Cell Biochem 2011;357:171-179.
74 Lang PA, Beringer O, Nicolay JP, Amon O, Kempe DS, Hermle T, Attanasio P, Akel A, Schafer R, Friedrich B, Risler T, Baur M, Olbricht CJ, Zimmerhackl LB, Zipfel PF, Wieder T, Lang F: Suicidal death of erythrocytes in recurrent hemolytic uremic syndrome. J Mol Med (Berl) 2006;84:378-388.
75 Nicolay JP, Schneider J, Niemoeller OM, Artunc F, Portero-Otin M, Haik G, Jr., Thornalley PJ, Schleicher E, Wieder T, Lang F: Stimulation of suicidal erythrocyte death by methylglyoxal. Cell Physiol Biochem 2006;18:223-232.
76 Lang E, Gatidis S, Freise NF, Bock H, Kubitz R, Lauermann C, Orth HM, Klindt C, Schuier M, Keitel V, Reich M, Liu G, Schmidt S, Xu HC, Qadri SM, Herebian D, Pandyra AA, Mayatepek E, Gulbins E, Lang F, Haussinger D, Lang KS, Foller M, Lang PA: Conjugated bilirubin triggers anemia by inducing erythrocyte death. Hepatology 2015;61:275-284.
77 Kempe DS, Akel A, Lang PA, Hermle T, Biswas R, Muresanu J, Friedrich B, Dreischer P, Wolz C, Schumacher U, Peschel A, Gotz F, Doring G, Wieder T, Gulbins E, Lang F: Suicidal erythrocyte death in sepsis. J Mol Med (Berl) 2007;85:273-281.
78 Lang PA, Schenck M, Nicolay JP, Becker JU, Kempe DS, Lupescu A, Koka S, Eisele K, Klarl BA, Rubben H, Schmid KW, Mann K, Hildenbrand S, Hefter H, Huber SM, Wieder T, Erhardt A, Haussinger D, Gulbins E, Lang F: Liver cell death and anemia in Wilson disease involve acid sphingomyelinase and ceramide. Nat Med 2007;13:164-170.
79 Jilani K, Qadri SM, Lang F: Geldanamycin-induced phosphatidylserine translocation in the erythrocyte membrane. Cell Physiol Biochem 2013;32:1600-1609.
80 Vota DM, Maltaneri RE, Wenker SD, Nesse AB, Vittori DC: Differential erythropoietin action upon cells induced to eryptosis by different agents. Cell Biochem Biophys 2013;65:145-157.
81 Zappulla D: Environmental stress, erythrocyte dysfunctions, inflammation, and the metabolic syndrome: adaptations to CO2 increases? J Cardiometab Syndr 2008;3:30-34.
82 Zbidah M, Lupescu A, Jilani K, Lang F: Stimulation of suicidal erythrocyte death by fumagillin. Basic Clin Pharmacol Toxicol 2013;112:346-351.
83 Abed M, Herrmann T, Alzoubi K, Pakladok T, Lang F: Tannic Acid induced suicidal erythrocyte death. Cell Physiol Biochem 2013;32:1106-1116.
84 Ghashghaeinia M, Cluitmans JC, Toulany M, Saki M, Koberle M, Lang E, Dreischer P, Biedermann T, Duszenko M, Lang F, Bosman GJ, Wieder T: Age Sensitivity of NFkappaB Abundance and Programmed Cell Death in Erythrocytes Induced by NFkappaB Inhibitors. Cell Physiol Biochem 2013;32:801-813.
85 Alzoubi K, Honisch S, Abed M, Lang F: Triggering of Suicidal Erythrocyte Death by Penta-O-galloyl-beta-d-glucose. Toxins (Basel) 2014;6:54-65.
86 Jilani K, Lang F: Carmustine-induced phosphatidylserine translocation in the erythrocyte membrane. Toxins (Basel) 2013;5:703-716.
87 Jilani K, Enkel S, Bissinger R, Almilaji A, Abed M, Lang F: Fluoxetine induced suicidal erythrocyte death. Toxins (Basel) 2013;5:1230-1243.
88 Lupescu A, Bissinger R, Jilani K, Lang F: Triggering of suicidal erythrocyte death by celecoxib. Toxins (Basel) 2013;5:1543-1554.

89 Lupescu A, Jilani K, Zbidah M, Lang F: Patulin-induced suicidal erythrocyte death. Cell Physiol Biochem 2013;32:291-299.
90 Abed M, Zoubi KA, Theurer M, Lang F: Effect of dermaseptin on erythrocytes. Basic Clin Pharmacol Toxicol 2013;113:347-352.
91 Arnold M, Lang E, Modicano P, Bissinger R, Faggio C, Abed M, Lang F: Effect of nitazoxanide on erythrocytes. Basic Clin Pharmacol Toxicol 2014;114:421-426.
92 Oswald G, Alzoubi K, Abed M, Lang F: Stimulation of suicidal erythrocyte death by ribavirin. Basic Clin Pharmacol Toxicol 2014;114:311-317.
93 Alzoubi K, Calabrò S, Bissinger R, Abed M, Faggio C, Lang F: Stimulation of Suicidal Erythrocyte Death by Artesunate. Cell Physiol Biochem 2014;34:2232-2244.
94 Arnold M, Bissinger R, Lang F: Mitoxantrone-induced suicidal erythrocyte death. Cell Physiol Biochem 2014;34:1756-1767.
95 Bissinger R, Fischer S, Jilani K, Lang F: Stimulation of Erythrocyte Death by Phloretin. Cell Physiol Biochem 2014;34:2256-2265.
96 Bissinger R, Modicano P, Frauenfeld L, Lang E, Jacobi J, Faggio C, Lang F: Estramustine-induced suicidal erythrocyte death. Cell Physiol Biochem 2013;32:1426-1436.
97 Jacobi J, Lang E, Bissinger R, Frauenfeld L, Modicano P, Faggio C, Abed M, Lang F: Stimulation of erythrocyte cell membrane scrambling by mitotane. Cell Physiol Biochem 2014;33:1516-1526.
98 Lupescu A, Bissinger R, Herrmann T, Oswald G, Jilani K, Lang F: Induction of suicidal erythrocyte death by novobiocin. Cell Physiol Biochem 2014;33:670-680.
99 Malik A, Bissinger R, Calabro S, Faggio C, Jilani K, Lang F: Aristolochic Acid Induced Suicidal Erythrocyte Death. Kidney Blood Press Res 2014;39:408-419.
100 Tesoriere L, Attanzio A, Allegra M, Cilla A, Gentile C, Livrea MA: Oxysterol mixture in hypercholesterolemia-relevant proportion causes oxidative stress-dependent eryptosis. Cell Physiol Biochem 2014;34:1075-1089.
101 Zhang R, Xiang Y, Ran Q, Deng X, Xiao Y, Xiang L, Li Z: Involvement of calcium, reactive oxygen species, and ATP in hexavalent chromium-induced damage in red blood cells. Cell Physiol Biochem 2014;34:1780-1791.
102 Pagano M, Faggio C: The use of erythrocyte fragility to assess xenobiotic cytotoxicity. Cell Biochem Funct 2015;33:351-355.
103 Borst O, Abed M, Alesutan I, Towhid ST, Qadri SM, Foller M, Gawaz M, Lang F: Dynamic adhesion of eryptotic erythrocytes to endothelial cells via CXCL16/SR-PSOX. Am J Physiol Cell Physiol 2012;302:C644-C651.
104 Andrews DA, Low PS: Role of red blood cells in thrombosis. Curr Opin Hematol 1999;6:76-82.
105 Chung SM, Bae ON, Lim KM, Noh JY, Lee MY, Jung YS, Chung JH: Lysophosphatidic acid induces thrombogenic activity through phosphatidylserine exposure and procoagulant microvesicle generation in human erythrocytes. Arterioscler Thromb Vasc Biol 2007;27:414-421.
106 Zwaal RF, Comfurius P, Bevers EM: Surface exposure of phosphatidylserine in pathological cells. Cell Mol Life Sci 2005;62:971-988.
107 Closse C, Dachary-Prigent J, Boisseau MR: Phosphatidylserine-related adhesion of human erythrocytes to vascular endothelium. Br J Haematol 1999;107:300-302.
108 Gallagher PG, Chang SH, Rettig MP, Neely JE, Hillery CA, Smith BD, Low PS: Altered erythrocyte endothelial adherence and membrane phospholipid asymmetry in hereditary hydrocytosis. Blood 2003;101:4625-4627.
109 Pandolfi A, Di Pietro N, Sirolli V, Giardinelli A, Di Silvestre S, Amoroso L, Di Tomo P, Capani F, Consoli A, Bonomini M: Mechanisms of uremic erythrocyte-induced adhesion of human monocytes to cultured endothelial cells. J Cell Physiol 2007;213:699-709.
110 Wood BL, Gibson DF, Tait JF: Increased erythrocyte phosphatidylserine exposure in sickle cell disease: flow-cytometric measurement and clinical associations. Blood 1996;88:1873-1880.