3.3. Eribulin Induces Molecular Markers of DNA Damage and Apoptosis in Acute Myeloid and Lymphoid Leukemia Cells

At the molecular level, the analyses of STMN1 and its inactive form (p-STMN1^{S16}) (proliferation marker), γH2AX (DNA damage marker), and the cleaved PARP1 (apoptosis marker) levels were evaluated. At low eribulin concentrations, an induction of STMN1 phosphorylation was observed, while at high concentrations, the STMN1 expression was downregulated (all $p < 0.05$). Additionally, the eribulin exposure significantly induced γH2AX expression and PARP1 cleavage in all of the cell lines analyzed (Figure 6).

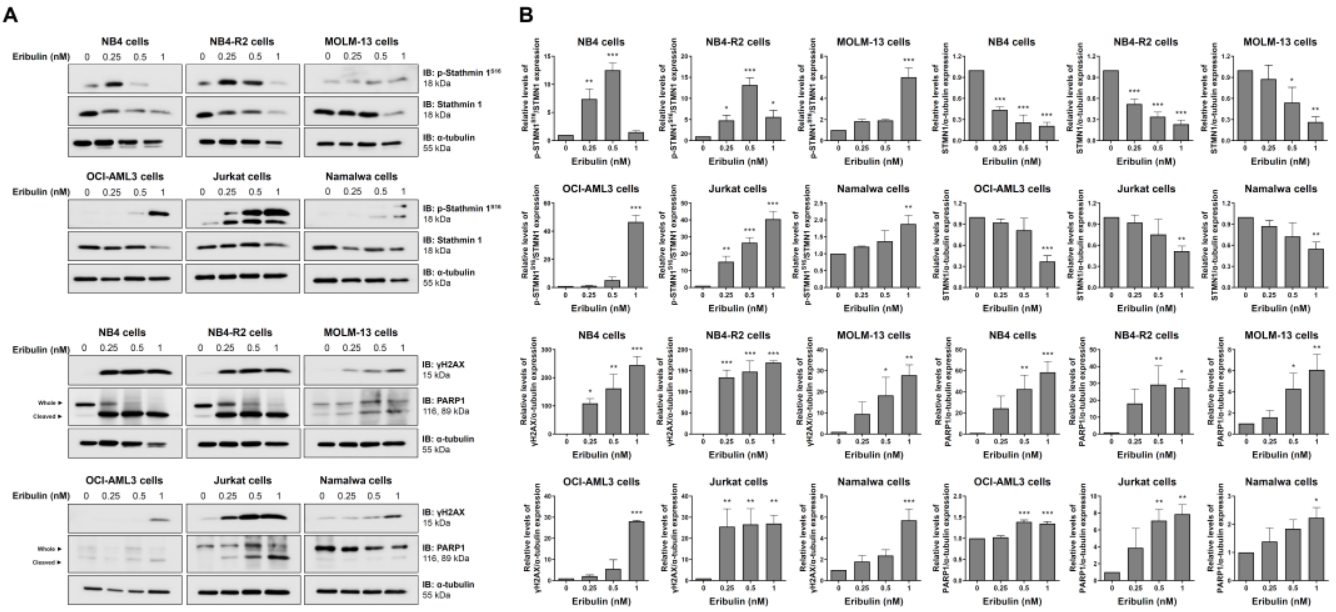

Figure 6. Eribulin induces molecular markers of DNA damage and apoptosis in acute leukemia cells. (**A**) Western blot analysis for levels of phospho(p)-STMN1^{S16}, STMN1, γH2AX, and PARP1 (total and cleaved) in total cell extracts of vehicle- and eribulin-treated acute leukemia cells (0.25, 0.5, and 1 nM) for 48 h; Membranes were incubated with the indicated antibodies and developed with the SuperSignal West Dura Extended Duration Substrate System and images were acquired with a Gel Doc XR+. (**B**) Bar graphs represent the mean ± SD of three independent experiments quantifying the indicated protein band intensities. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ANOVA and Bonferroni post-test.

3.4. P-Glycoprotein and NFκB-Mediated Pathways Are Related to Eribulin Resistance in Hematologic Malignancies

Next, we evaluated whether the already known response biomarkers for solid tumors could be applied in the context of hematologic malignancies [19–24]. First, we determined the expression of the genes encoding the transmembrane drug efflux pump (ABCB1 and ABCC1), which encodes tubulin beta 3 class III (TUBB3) and STMN1 (Figure 7A) and the markers PI3K/AKT and NFkB-mediated signaling pathway expression and activation (Figure 7B,C). Among these molecular targets, ABCB1 (r = 0.53, $p = 0.02$), ABCC1 (r = 0.67, $p = 0.001$), p-AKT (r = 0.53, $p = 0.02$), p-NFκB (r = 0.80, $p < 0.0001$), and NFκB (r = 0.81, $p < 0.0001$) were associated with IC_{50} values for eribulin in the blood cancer cell lines (Figure 7D). Based on these data, we constructed a resistance eribulin-related target (RERT) score that precisely predicted the sensitivity of the drug in the cellular models evaluated (Figure 7E).

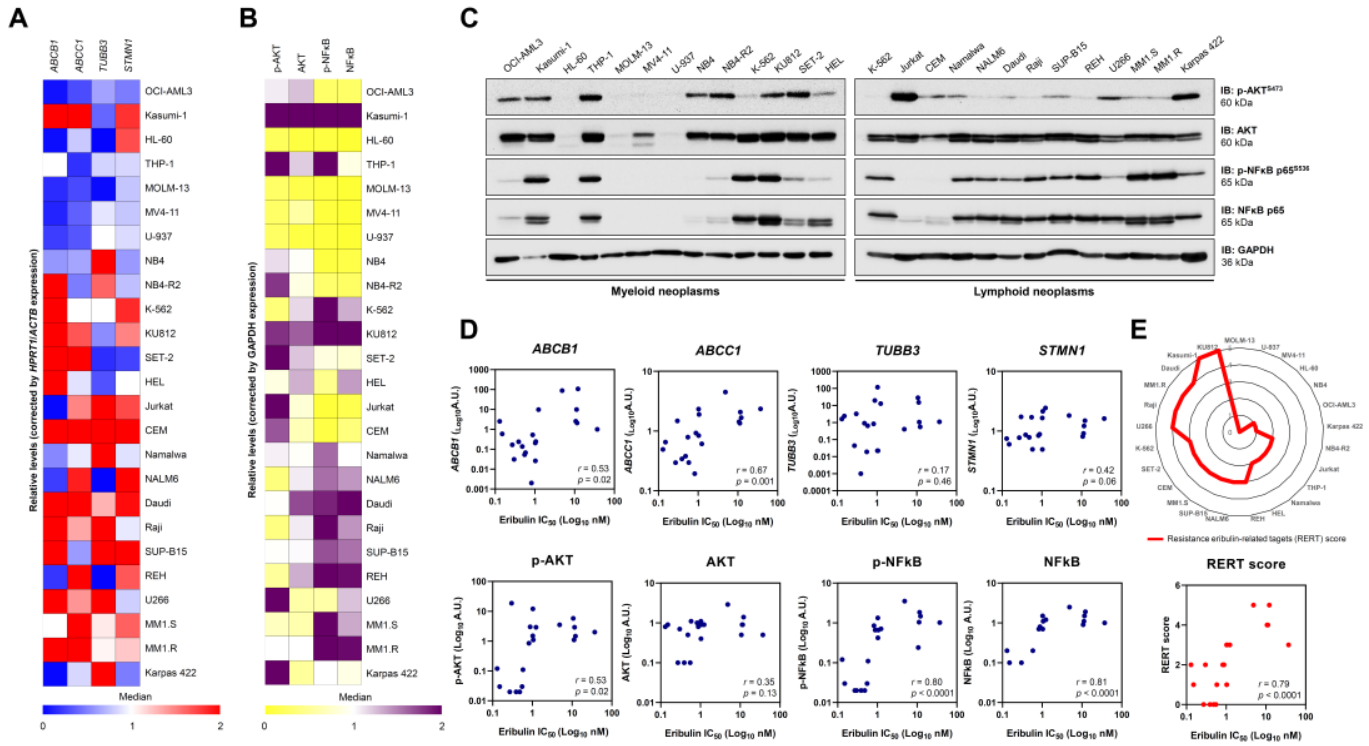

Figure 7. Resistance to eribulin is associated with the high expression/activation of MDR1, NFκB, and AKT in blood cancer cells. The heatmaps illustrate the expression of genes (**A**) or proteins (**B**) associated with resistance to eribulin in a panel of hematologic neoplasm cell lines. Gene data are represented as relative expression corrected by *HPRT1*/*ACTB* expression. Downregulated and upregulated genes are given by blue and red, respectively. Protein expression data are represented as relative levels corrected by the expression of GAPDH. Downregulated and upregulated proteins are indicated by yellow and purple, respectively. (**C**) Representative Western blot analysis for phospho(p)-AKT^{S473}, AKT, (p)-NFκB p65^{S536}, and NFκB p65 in total cell extracts from myeloid and lymphoid neoplasms cell lines. (**D**) Correlation graphs between expression of *ABCB1*, *ABCC1*, *TUBB3*, *STMN1*, p-AKT, AKT, p-NFκB, or NFκB and IC_{50} values for eribulin in blood cancer cells. (**E**) Using molecular markers that significantly correlate with IC_{50} to eribulin in hematologic neoplasms, a resistance eribulin-related targets (RERT) score was created, in which each cell line receives one point for each gene/protein upregulated (the median was used as the cutoff; the maximum number of points = 5). The radar graph shows the distribution of points among the analyzed cell lines. We note that the score precisely correlated with the drug's sensitivity in the cellular models evaluated.

Finally, using the pharmacological inhibitors of P-glycoprotein (elacridar) and NFκB (PDTC), we observed that the resistance conferred by the drug efflux pump, but not NFκB activation, is reversible, and it can eliminate a leukemia cell model with the activation of both of the molecular processes (Figure 8). Combining eribulin and elacridar was not toxic to the normal leukocytes (Figure S3).

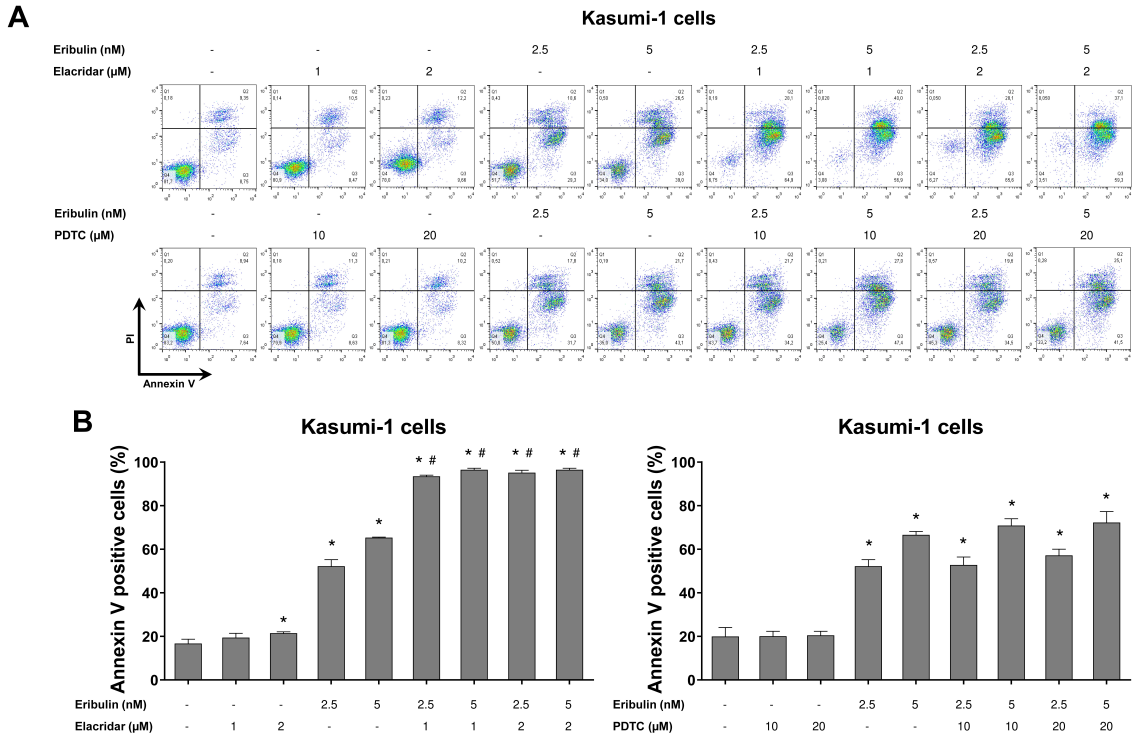

Figure 8. Elacridar, a P-glycoprotein inhibitor, potentiates eribulin-induced apoptosis in Kasumi-1 cells. (**A**) Apoptosis was detected by flow cytometry using APC-annexin V and propidium iodide staining. Representative dot plots are counters for each condition; the upper and lower right quadrants cumulatively the apoptotic population (annexin V^+ cells). (**B**) Bar graphs represent the mean ± SD of at least three independent experiments quantifying apoptotic cell death in Kasumi-1 cells after exposure to the vehicle, eribulin (2.5 and 5 nM) and/or elacridar (1 and 2 μM) and/or PDTC (10 and 20 μM) for 72 h. The *p* values are indicated in the graphs; * $p < 0.05$ for eribulin-, elacridar-, and/or PDTC-treated cells vs. vehicle-treated cells, # $p < 0.05$ for eribulin-, elacridar-, or PDTC-treated cells versus combination treatment at the corresponding doses; ANOVA and Bonferroni post-test.

4. Discussion

Here, we investigated eribulin's cellular and molecular effects in a molecularly heterogeneous panel of hematologic neoplasm cell lines, including acute myeloid leukemia, myeloproliferative neoplasms, acute lymphoblastic leukemia, multiple myeloma, and lymphoma models. Eribulin is a simplified synthetic analog of halichondrin B, a molecule isolated from a rare marine sponge *Halichondria okadai* [25,26]. It is currently approved for pre-treated and anthracycline- and taxane-refractory patients with metastatic breast cancer and metastatic liposarcoma [27,28]. In the context of hematologic malignancies, our study is pioneering, and it opens the possibility of using eribulin for the patients with these diseases.

Eribulin is a microtubule inhibitor, and it exerts its anticancer property primarily through the inhibition of tubulin and mitosis [29–32]. Unlike other antimitotic drugs, such as vinblastine and paclitaxel, which attenuate the shortening and growth phases of dynamic microtubule instability, eribulin inhibits microtubule growth by a final poisoning mechanism [29]. Thus, it does not cause the shortening of the tubulin, but it transforms them into non-productive aggregates [29].

In the present study, eribulin presented a high cytotoxic effect in blood cancer cells with minimal impact on the normal leukocytes. In agreement, eribulin has been reported to be a powerful chemotherapeutic agent with a low-to-moderate toxicity profile [33]. The cellular phenotype observed for the eribulin treatment in the leukemia cells indicated that

the drug's primary cellular mechanism of action is conserved: cell cycle blockage in G_2/M and cell death after prolonged and irreversible mitotic arrest [29,34–36].

Molecularly, eribulin reduced the expression and activity of STMN1, and induced PARP1 cleavage and H2AX phosphorylation. STMN1 functions as a marker of normal and malignant hematopoietic cell proliferation, and it plays a key role in cell cycle progression and clonogenicity in acute leukemia cells [37–39]. Recently, STMN1 expression has been indicated as a molecular target of eribulin and associated with the response to the drug [24]. PARP1 is one of the cellular substrates of caspases, and when it is cleaved and inactivated by active caspases 3 and 7, it is considered to be a hallmark of apoptosis, forming 24 kDa and 89 kDa fragments [40,41]. H2AX is a component of the histone octamer in nucleosomes that, in the presence of DNA damage, are phosphorylated at serine 139 (i.e., γH2AX), thus making it a DNA damage marker [42]. Overall, the molecular scenario of treating acute leukemia cells with eribulin yielded reduced cell proliferation, apoptosis, and DNA damage.

Despite their importance to the antineoplastic arsenal, antimicrotubule agents present various resistance mechanisms that may lead to treatment failure and reduced survival rates [43]. Thus, understanding eribulin-related resistance mechanisms may improve the response rates. Over the last few years, several mechanisms have been reported, particularly the activation of P-glycoprotein and pathways mediated by PI3K/AKT and NFκB [19–23,44]. Indeed, in the present study, the sensitivity to eribulin was associated with the *ABCB1*, *ABCC1*, p-AKT, p-NFκB, and NFκB expression levels in the blood cancer cells.

The multidrug resistance (MDR) phenotype is a challenge in the therapeutic management of several neoplasms since cancer cells become unresponsive to many anticancer drugs [45,46]. Several cellular and molecular mechanisms mediate this complex process, and one of the most explored ones is the enhancement of drug efflux transporters that are responsible for reducing intracellular drug concentration [46–49]. Previous studies have associated the overexpression of subfamily B of the ATP-binding cassette members with eribulin resistance [19,20,50].

Activating the PI3K/AKT/mTOR pathway contributes to tumor development and a resistance to anticancer therapies [51]. A previous study reported that the activation of the PI3K/AKT pathway induces the primary resistance or early adaptation to eribulin in HER2-negative breast cancer models [44]. Similarly, the upregulation of the NFκB pathway increased eribulin resistance in breast cancer models [22,23]. Given that the TIMP1/CD63/PI3K/AKT/p21 axis has been described as a molecular mechanism that promotes leukemia cell proliferation and survival [52], we investigated whether *TIMP1* expression could be associated with eribulin resistance, but we detected no association (Figure S4).

In our study, the combined treatment of eribulin and elacridar significantly increased eribulin-induced apoptosis in drug-resistant leukemia cells. Interestingly, previous studies reported that elacridar improved the response to other chemotherapy agents. For example, in chronic myeloid leukemia, combining elacridar with imatinib attenuated the drug efflux transporter-associated resistance [53]. Moreover, elacridar overcame resistance to topoisomerase inhibitors in small-cell lung [54] and gastric [55] cancers. Additionally, in prostate cancer, it was demonstrated that the resistance to olaparib might also be overcome using elacridar [56]. Furthermore, the highly eribulin-resistant KBV20C oral cancer cells were shown to be sensitized by a co-treatment with a low dose of elacridar [57].

5. Conclusions

In summary, our data indicate that eribulin disrupts the microtubule dynamics and leads to mitotic catastrophe and cell death in blood cancer cells. The expression and activation of the MDR1, PI3K/AKT, and NFκB-related targets may be biomarkers of the eribulin response in hematologic malignancies. Additionally, the combined treatment of eribulin plus elacridar may overcome drug resistance in these diseases. Future studies must determine if eribulin can be repositioned to treat blood cancers.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers14246080/s1, Figure S1: Whole gel images related to Figure 6; Figure S2: Whole gel images related to Figure 7; Figure S3: The combination of eribulin and elacridar does not impact the cell viability of normal leukocytes; Figure S4: Correlation between TIMP1 and response to eribulin in blood cancer cells; Table S1: Primer sequences and concentrations; Table S2: Cell lines' characteristics and their sensitivity to eribulin.

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Institutional Review Board Statement: All procedures used were approved by the Ethics Committee of the Ethical Committee of the Institute of Biomedical Sciences of the University of São Paulo (CAAE:39510920.1.0000.5467). Informed was obtained from all healthy donors, and it was approved by the Research Ethics as described in the section consent to participate in ethics approval and consent to participate. All methods were conducted in accordance with the approved guidelines and the Declaration of Helsinki.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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