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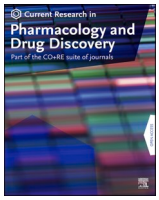

Mechanistic update of Trisenox in blood cancer

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ABSTRACT

Acute promyelocytic leukemia (APL)/blood cancer is M3 type of acute myeloid leukemia (AML) formed inside bone marrow through chromosomal translocation mutation usually between chromosome 15 & 17. It accounts around 10% cases of AML worldwide. Trisenox (TX/ATO) is used in chemotherapy for treatment of all age group of APL patients with highest efficacy and survival rate for longer period. High concentration of TX inhibits growth of APL cells by diverse mechanism however, it cures only PML-RARα fusion gene/oncogene containing APL patients. TX resistant APL patients (different oncogenic make up) have been reported from worldwide. This review summarizes updated mechanism of TX action via PML nuclear bodies formation, proteasomal degradation, autophagy, p53 activation, telomerase activity, heteromerization of pRb & E2F, and regulation of signaling mechanism in APL cells. We have also provided important information of combination therapy of TX with other molecules mechanism of action in acute leukemia cells. It provides updated information of TX action for researcher which may help finding new target for further research in APL pathophysiology or new TX resistant APL patients drug designing.

1. Introduction

APL is M3 subtype of AML accounts around 5–10% of AML patients cases (Sant et al., 2010). It forms inside bone marrow due to chromosomal translocation mutation usually between chromosome 15 and 17 leading to formation of fusion gene (oncogene) PML-RARα and RARα -PML. PML-RARα is responsible for the pathogenesis of APL and RARα -PML will be used important molecular marker for monitoring of APL patients (Kumar et al., 2018a). TX and all trans retinoic acid (ATRA) combination had been used for treatment of both low and intermediate risk APL patients and achieved fantastic success with improved complete remission (CR) rate around 90–95% (Shen et al., 2004; Lo-Coco et al., 2013). They work in targeted therapy by induction of differentiation, maturation of promyelocytes, eradication of leukemia -initiating cells, cell cycle arrest, apoptosis, and finally degradation of PML-RARα in APL patients (Zheng et al., 2005; Giannì et al., 1998; Dos Santos et al., 2013; Nasr et al., 2008). ATO and ATRA combination have been also worked successfully in old and cardiovascular complications APL patients (Lo-Coco et al., 2013) but not provide good outcomes in high-risk refractory APL patients and RA-resistant promyelocytic leukemia zinc finger (PLZF-RARα) patients (Ablain et al., 2014; Coombs et al., 2015; Sanz and Lo-Coco, 2011; Zhou et al., 2007). However, TX and ATRA combination treated APL patients will be experienced the ATRA syndrome and other cardiovascular complications (de Botton et al., 2003). Therefore, TX has been emerged a new drug for treatment of all age relapsed or refractory APL patients in both induction and consolidation therapy as well as high-risk APL patients. It also works in combination with ATRA and idarubicin, with highest CR (~99 %) rate for prolonged survival period (Coombs et al., 2015; Sanz and Lo-Coco, 2011; Zhou et al., 2007; Kumar et al., 2014). TX enters APL cells through diffusion (Kumar et al., 2018a) and bound to cysteine residues on the PML moiety of the PML-RARα or PML to formed PML nuclear bodies and undergoes ubiquitination as well as proteasomal degradation (Dos Santos et al., 2013). It also works by diverse mechanism inside APL cells for instance, production of reactive oxygen species (ROS), oxidative stress, DNA damage, cell cycle regulation, and apoptosis (Kumar et al., 2014, 2018a; Dos Santos et al., 2013; Miller et al., 2002). TX is effective treatment of only fusion gene/oncogene (PML-RARα) containing APL patients but it gets resistant to other fusion gene (PLZF-RARα) containing APL patients (Rego et al., 2000). TX resistant APL patients have been reported worldwide continuously (Tomita et al., 2013; Lou et al., 2015). TX toxicity is enhanced by drugs/inhibitors to kill cancer cells. This review summaries the updated mechanism of action of TX in APL cells which

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List of abbreviations:

APL	Acute Promyelocytic Leukemia
TX	Trisenox/Arsenic Trioxide
ATRA	All trans retinoic acid
P53	Tumor suppressor protein
pRb	Retinoblastoma protein
E2F1	E2 promoter binding factor
PML	Promyelocytic Leukemia
PTEN	Phosphatase and tensin homolog, deleted on chromosome TEN
PML-RARα	Fusion protein/oncogene
PLZF-RARα	Retinoic acid -resistant promyelocytic leukemia zinc finger
CR	Complete remission
DAXX	Death-associated protein 6
HAUSP	Herpesvirus-associated ubiquitin-specific protease
MDM2	Mouse double minute 2 homolog
ATM	Ataxia-telangiectasia mutated
ATR	Ataxia telangiectasia and Rad3 related
UBC9	Ubiquitin-conjugating enzyme 9
RNF4	Ring finger protein 4
SUMO	Small ubiquitin-like modifier

may help researcher to find novel TX target of action for further continued research or new antileukemic drug designing for treatment of TX resistant APL patients (see Figs. 1–4).

2. TX induces PML nuclear bodies formation, sumoylation, ubiquitination, and proteasomal degradation

TX induces degradation of both the PML-RARα fusion protein and the normal PML protein in APL cells (Vitaliano-Prunier et al., 2014). It binds to cysteine residues on the PML moiety of the fusion protein and induced formation of PML nuclear bodies (PMLNBs), a subnuclear domains regulated cellular stress responses, cell cycle, apoptosis, and senescence (Dos Santos et al., 2013). TX also triggers the binding of ubiquitin-conjugating enzyme 9 (UBC9) in the PML RING finger domain leading to PML-RARα moiety to undergo sumoylation. RNF4 (ring finger protein 4) is a SUMO-dependent ubiquitin ligase attached to PMLNBs and polyubiquitylated PML leading to proteasomal degradation (Vitaliano-Prunier et al., 2014; Lallemand-Breitenbach et al., 2008; Tatham et al., 2008). Sumoylation is an addition of small ubiquitin-like modifier (SUMO) on protein which would dynamic and reversible post-translational modification of protein. It involves in regulation of cell cycle progression, DNA damage, apoptosis, and ubiquitin mediated proteasome degradation (Han et al., 2018; Widagdo et al., 2012; Kukkula et al., 2021). Existing evidence suggested that TX-induced apoptosis in hypersumoylated PML of PML-RARα by PIC-1/SUMO-1 in NB4 and U937 cells (Sternsdorf et al., 1999). It is SUMOylated on Lys 160 residue of PML by SUMO-2 and facilitated RNF4 binding leading to triggered-ubiquitin mediated degradation of the PML-RARα (Lallemand-Breitenbach et al., 2008). PML degradation is also required C-terminal SUMO Interacting Motif (SIM) (Maroui et al., 2012). TX induces degradation of PML-RARα by enhancing UBE2I-mediated sumoylation and down regulation of PCGF2, a polycomb group protein in NB4 cells. TX-induced PML-RARα degradation is negatively regulated by PCGF2. PCGF2 Knockdown NB4 cells undergo sumoylation-, ubiquitylation- and PML nuclear body-mediated degradation of PML-RARα protein without ATO treatment (Jo et al., 2016). It has been reported that TX directly bound to cysteine residue in Zinc finger domain of PML-RARα fusion protein which assisted in the recruitment of SUMO-conjugating enzyme (UBC9) and triggering PML degradation (Zhang et al., 2010). PAIS1 is a SUMO-E3 ligase enzyme involved in sumoylation of PML and PML-RARalpha in NSCLC and APL through CK2 mediated phosphorylation and ubiquitin mediated degradation of PML (Rabellino et al., 2012). TX forms ROS -initiated intermolecular disulfide bond with PML and nuclear bodies leading to sumoylation and degradation of PML (Jeanne et al., 2010). Ki-1/57 is a nucleus and cytoplasmic regulatory protein exist in cancer cells. Sumoylation of Ki-1/57 is regulated through PMLNBs formed by TX (Saito et al., 2017).

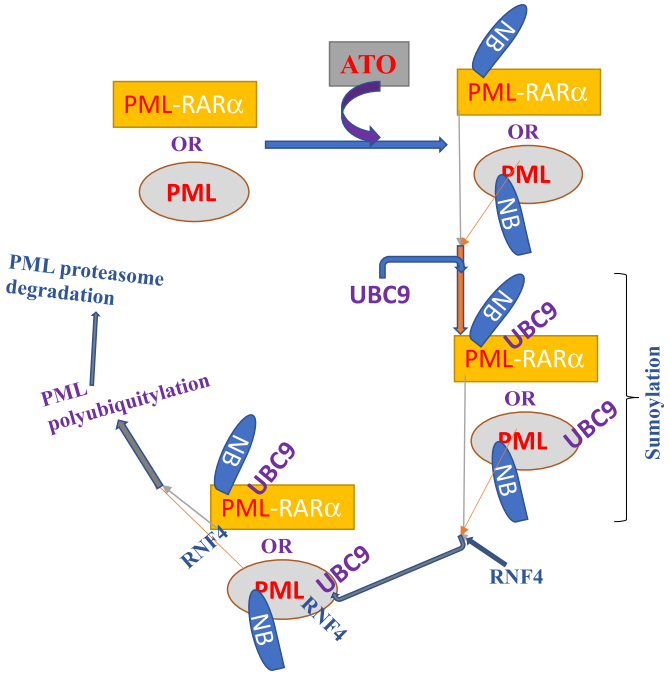
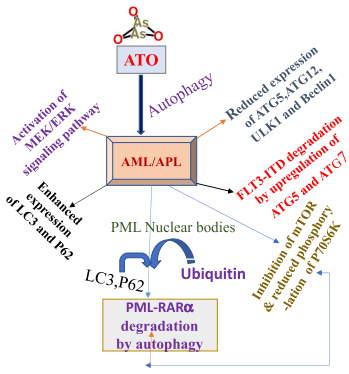


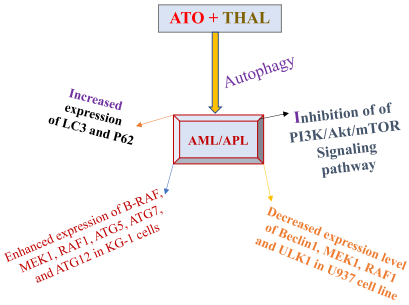
Fig. 1. TX induced PML degradation: TX enters into APL cells through diffusion and binds to PML to formed PML nuclear bodies undergoes sumoylation, ubiquitylation, and finally proteasomal degradation in APL cells.

3. TX causes autophagy

Autophagy is an intracellular catabolic pathway in which cellular content (proteins and organelles) delivered for degradation/recycling by autophagosomes/lysosomes. It should novel target for cancer treatment (Yang and Klionsky, 2020; Levy et al., 2017). TX induces autophagy in acute leukemia cells through activation of MEK/ERK pathway in primary hematopoietic progenitors of AML patients. Existing evidence suggested that pharmacological inhibitor of autophagy reversed TX action targeting beclin 1 or Atg 7 in leukemia cells (Zhang et al., 2013; Goussetis et al., 2010). It inhibits mechanistic target of rapamycin [mTOR] (a negative regulator of autophagy) and reduced phosphorylated form of P70S6 K, an autophagy inducer, facilitated PML-RARa degradation in APL cells (Moosavi and Djavaheri-Mergny, 2019). TX and THAL promote autophagy by inhibition of PI3K/Akt/mTOR signaling pathway in AML cells. They enhance expression of autophagy markers, LC3 and P62 by decreased expression level of Beclin1, MEK1, RAF1 and ULK1 in U937 cell line. ATO and THAL decrease expression level of autophagy activators, Beclin1, ULK1 by increased expression of LC3 –II (an autophagosomes marker) in KG-1 cells. They are also enhanced expression of B-RAF, MEK1, RAF1, ATG5, ATG7, and ATG12 in KG-1 cells (Kian et al., 2020). TX causes degradation of Fms-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) oncoprotein by autophagy-dependent degradation mediated through upregulation of ATG5 and ATG7 in AML. Interestingly, the co-localization of P62/SQSTML with FLT3-ITD oncoprotein aggregates autophagy and subsequently delivered FLT3-ITD oncoprotein into the lysosomal autophagy degradation (Liu et al., 2020; Yousefnia, 2021). TX stimulates



A. TX –induced autophagy: TX causes autophagy in AML/APL through activation of MEK/ERK signaling pathway, inhibition of mTOR, & PML-RARα degradation.



B. TX & THAL induce autophagy in AML/APL: they inhibit Beclin1, MEK1, RAF1 ULK1, and PI3K/Akt/mTOR signaling pathway by enhancing autophagic markers, LC3 and p62.

Fig. 2. A. TX –induced autophagy: TX causes autophagy in AML/APL through activation of MEK/ERK signaling pathway, inhibition of mTOR, & PML-RARα degradation. B. TX & THAL induce autophagy in AML/APL: they inhibit Beclin1, MEK1, RAF1 ULK1, and PI3K/Akt/mTOR signaling pathway by enhancing autophagic markers, LC3 and p62.

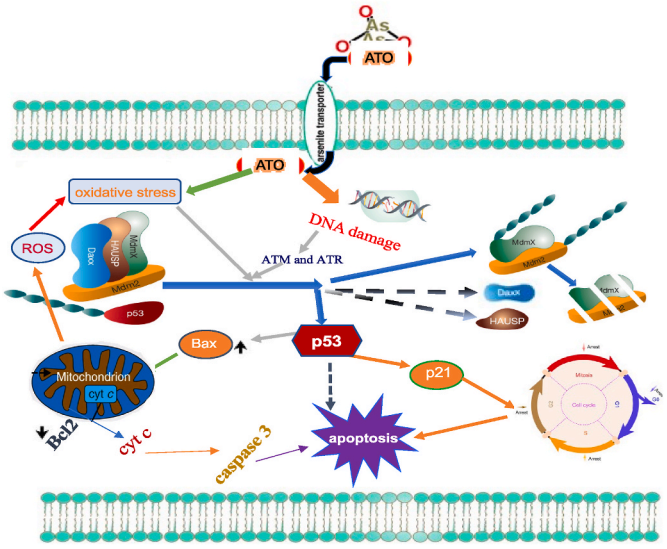


Fig. 3. TX activates tumor suppression protein: It reduces MDM2-DAXX-HAUSP complex proteins expression leading to p53 activation, cell cycle regulation and apoptosis in APL cells.

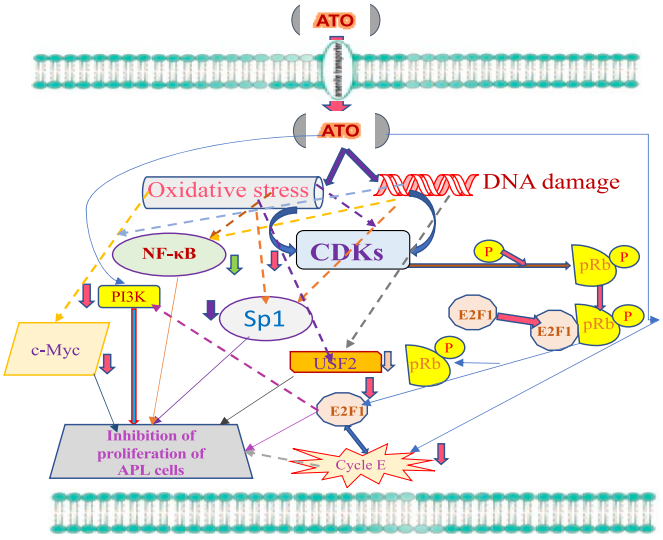


Fig. 4. TX regulates tumor and transcriptional proteins association: TX regulates growth of APL cells through transcriptional factors (E2F1, NF-kB, Sp1 and c-Myc) and its heteromerization with phosphorylated tumor protein at different residues.

expression of autophagosome elongation autophagy marker, LC3 and P62 by reduced expression levels of autophagy initiators, for instance ATG5, ATG12, ULK1, and Beclin1in AML It is also induced binding of ubiquitin on PML nuclear bodies to facilitated autophagic degradation of PML with colonization of ubiquitin, P62, LC3, and co-localization of PML-RARα to P62/SQSTM1 (an autophagy adaptor) mediated autophagy degradation in AML (Zhang et al., 2013; Yousefnia, 2021). TX enhances ETosis (a novel cell death pathway) in NB4 cells at moderate concentrations (0.5–0.75 μM) through mammalian target of rapamycin (mTOR)-dependent autophagy, which is partially regulated by reactive oxygen species (Li et al., 2018).

4. TX modulates tumor suppressor gene

Tumor suppressor gene gets less expressed or mutated in cancer cells which is regulated cell cycle, apoptosis and genomic integrity. TX-induced oxidative stress and genotoxicity are transmitted by protein kinases (ATM & ATR) and its downstream target CHK1 & CHK2 phosphorylation at Ser 345, Thr68, Ser 1981 and Ser 428 residues leading to activation of p53 b y reduced expression of MDM2-DAXX-HAUSP complex proteins in acute leukemia cells. TX-induced activated p53 is involved in cell cycle arrest and forced acute leukemia cells to undergo apoptosis (Kumar et al., 2018a; Vogelstein et al., 2000; Vousden and Lu, 2002). Promyelocytic leukemia (PML) is a tumor suppressor gene usually less expressed in cancer cells, TX directly binds at cysteine residue of PML through oxidation and formed PML NBs in acute leukemia cells that facilitated sumoylation, ubiquitination, and proteosome degradation. PMLNBs regulates cellular stress and involved in determination fate of cancer cells may undergo cell cycle, apoptosis or autophagy. PML also regulates cell growth, stress responses and tumor suppression along with the mechanistic target of rapamycin (mTOR) (Dos Santos et al., 2013; Gurrieri et al., 2004). Phosphatase and tensin homolog, deleted on chromosome TEN (PTEN) is a tumor suppressor gene and lipid phosphatase which dephosphorylated PIP3, a lipid product of PI3 kinase. It opposes activation of oncogenic,

PI3K/AKT/mTOR signaling pathways. PTEN is usually mutated or functionally inactivated tumor suppressor gene in cancer cells. (Alvarez-Garcia et al., 2019). TX regulates growth of multiple myeloma cells through inhibition of Notch signaling and upregulation of PTEN expression (Hu et al., 2013). Retinoblastoma tumor suppressor protein (pRb) is negative regulator of cell proliferation and control transcription. Generally, it gets loss of function/inactivated in most of cancer cells and may change in expression due to epigenetic/post-translational modification for instance, acetylation and phosphorylation. TX stimulates expression and phosphorylation of pRb in both KG1 and NB4 cells (Guzman et al., 2020; Kumar and Tchounwou, 2021).

5. TX regulates transcriptional factors

E2F1 is a transcriptional factor in E2 promoter binding factor (E2F) family involved in cell proliferation and differentiation. TX inhibits cell cycle progression by inhibiting E2F1 activity with interaction with pRb. E2F1 overexpression results uncontrolled cell proliferation leading to tumorigenesis and cancer. TX reduces expression of E2F1, cyclin E by stimulating pRb expression in KG1 and NB4 cells. It also phosphorylates pRb at S608 and T373 residues which promoted formation of heterodimer between E2F1 and pRb leading to inhibition of both PI3K signaling pathway and APL cells proliferation simultaneously (Kumar and Tchounwou, 2021; Sheldon, 2017). Arsenic trioxide is reduced STAT3 protein phosphorylation and activity in acute myeloid leukemia patients sample by altered phosphorylation and electrophoretic mobility of ZNF198/fibroblast growth factor receptor 1 and reduced kinase protein level (Wetzler et al., 2006). TX inhibits HL-60 cells growth by inducing cell death through downregulation of expression of transcriptional factors, Sp1, c-Myc, NF-κB, and USF2 (Zhang et al., 2015). Sp1, a transcription factor in NB4 cells get oxidized upon longer duration treatment of TX leading to reduced expression of hTERT, C17, and c-Myc genes associated with reactive oxygen species production in NB4 cells (Chou et al., 2005). 10,058-F4 (c-Myc inhibitor) and TX combination enhance anti-leukemic activity through reduced phosphorylation of IκB, downregulation of expression of the anti-apoptotic genes, and apoptosis in NB4 cells (Sayyadi et al., 2020). TX blocks c-Myc mediated terminal differentiation of HL-60 cells (Jiang et al., 2008). It inhibits NB4 cells growth and viability through deactivation of NFκβ and downregulation of Pin1-mediated NF-κB-dependent activation of telomerase and survivin (Ghaffari et al., 2012). TX helps in reducing ATRA treated APL cells side effects for instance ATRA syndrome by decreased NF-kappaB activation through enhanced apoptosis. It is also reversed ATRA-induced degradation of the NF-kappaB inhibitor IkappaB in APL cells (Mathieu and Besançon, 2006). TX inhibits DNA-binding activity of NF-kappaB composed of p65/p50 heterodimer by hindering degradation of IkappaB-alpha and the nuclear translocation of p65 as well as interrupting the binding of NF-kappaB with its consensus sequences in HL-60 cells (Han et al., 2005). It also inhibits proliferation and induced apoptosis in NB4 cells through suppression of NF-kappaB (Momeny et al., 2010). TX binds with heat shock protein 60 (Hsp60) and damage its refolding capacity leading to disruption of formation of Hsp60-p53 and Hsp60-survivin complexes which result degradation of both p53 and survivin in NB4 cells (Hu et al., 2021).

6. TX effects on telomeres and telomerase activity

The shortening of telomeres and activation of telomerase are important feature of cancer cells helped in cellular immortalization and tumor progress. It has been reported that late stage of acute leukemia patients became shorter telomere and higher activity of telomerase (Wang et al., 2010). Combination of TX and oligonucleotide-based molecule against human telomerase RNA template (hTR ASODN)/inhibitor have reduced NB4 survival through forced apoptotic cell death by activation of DNA damage response via up-regulation of p73 and ATM coupled with down-regulation of c-Myc (Asghari-Kia et al., 2017). ATO is suppressed growth and viability of APL cells through cytotoxicity via shortening of telomere length, reduced telomerase activity, and apoptosis. It also induced transcriptional repression of Pin1, survivin, c-Myc, hTERT, and PinX1 along with rise in p73 on mRNA level (Ghaffari et al., 2012). TX inhibits HL-60 growth through induction of apoptosis by suppression of expression of the human telomere reverse transcriptase (hTERT) [an enzyme for telomerase synthesis] and its promoter region located transcription factors, Sp1, c-Myc, NF-κB and USF2 both mRNA and protein level (Zhang et al., 2015).

7. TX regulates signaling pathway

TX binds thiol groups of cysteines in protein of cells and regulated cellular signaling pathways (Dilda and Hogg, 2007; Ramadan et al., 2009). It also inhibited NF-κβ signaling pathway through binding at Cys −179 residue of IKK-β (Kapahi et al., 2000) and activated ERK pathway which may be important for the induction of autophagy and degradation of the PML protein (Goussetis et al., 2010; Hayakawa and Privalsky, 2004). RSK signaling regulates TX -induced growth inhibition of AML cells. Pharmacological inhibitor or molecular disruption of RSK signaling results enhanced TX -induced apoptosis and growth inhibition of AML cells (Galvin et al., 2013). TX inhibits growth of APL cells through apoptosis by activation of c-jun N-terminal kinase (JNK) (Davison et al., 2004). It induces apoptosis in NB4 cells through inhibition of PI3K/Akt signaling pathway, upregulation of expression of Spl protein, and modulation of activation of p53 (Li et al., 2009). It activates p38 and deactivated ERK1 and ERK2 leading to induction of apoptosis while activation of JNK and inactivation of ERKs prevent apoptosis in NB4 cells (Iwama et al., 2001). TX induces apoptosis in acute myeloid leukemia (M2) -derived cell line, NKM-1 by stimulating c-Jun N-terminal and stress-activated protein kinase (JNK/SAP) pathway (Kajiguchi et al., 2003). It enhances MAPK signaling pathway through activation of ERK1/2(Thr-202/Tyr-204) and also both TX & ATRA lead to increased phosphorylation and activation of MEK (Ser-217/221) in HL-60 cells (Nayak et al., 2010). TX -induces cytotoxicity in HL-60 cells through activation of phosphorylation of p38 MAPK, JNK, and ERK1/2. It also causes cytotoxicity in KG1a cells by stimulation of phosphorylation of MAPK and ERK1/2 and reduced phosphorylation of JNK (Kumar et al., 2018b). TX activates small G-protein Rac1 and the alpha and beta isoforms of the p38 mitogen-activated protein (p38 MA P) kinase in leukemia cells and further findings confirmed using bone marrows from patients of chronic myelogenous leukemia (Verma et al., 2002). It induces apoptosis in both NB4 and U937 cells through activation of p38 MAPK signaling pathway and targeted degradation of its downstream target, mitogen-activated protein kinase (MAPK)-interacting kinase 1 (Mnk1) &2. Both Mnk1/2 regulates downstream phosphorylation of the eukaryotic initiation factor, elF4E at Ser-209 residue (Dolniak et al., 2008). JNK activation is essential for TX -induced growth inhibition through apoptosis in acute promyelocytic leukemia (APL) cells i.e., NB4 (Davison et al., 2004).

8. Combination therapy

The morbidity and mortality in conventional ATO therapy is a challenging task to deal with in clinical trials. Combination to TX with other cancer drugs might give new insights into the cure and understanding of the disease. TX toxicity is enhanced with combination of other drugs/molecules in various cancer cells. Few combinations of TX with drugs/molecules are discussed below.

8.1. TX & ATRA

TX and ATRA combination are highly used in targeted therapy without exposure of chemotherapy by induction of maturation of leukemic promyelocytes, apoptosis, and eradication of APL-initiating cells through degradation of PML-RARAα (Zheng et al., 2005; Giannì

et al., 1998; Dos Santos et al., 2013; Nasr et al., 2008). APL patients are treated with TX - ATRA combination therapy improved complete remission (CR) rate between around 90–95% with shorter in the rate of relapse (Shen et al., 2004). TX - ATRA combination has emerged standard care of both low and intermediate risk APL patients in consolidation therapy with possible best outcomes and perfect for both older and cardiovascular complicated APL patients (Lo-Coco et al., 2013). They perform relapse free APL patients treatment through demethylation of targeted genes for instance, RARβ *and TGM2* (Huynh et al., 2019). TX - ATRA synergistic action induces differentiation of HL-60 cells through augmentation of ATRA-induced RAF/MEK/ERK axis signaling (Nayak et al., 2010). They enhance cytotoxicity in HL-60 cells through prevention of Nrf2 nuclear translocation (activity) (Valenzuela et al., 2014). The ATRA + TX combination therapy is more effective for newly diagnosed APL patients with a higher CR rate however lower early mortality and relapse rate (Ma and Yang, 2015). They are preferred procedure for low-to-intermediate risk APL patients (Ma et al., 2016). A combination of TX with low-dose ATRA (LD-ATRA) give significantly better therapeutic outcomes for instance, lower mortality, a higher CR rate, and no worse toxic side-effects compare to either TX or ATRA alone in APL patients (Wang et al., 2004).

8.2. TX and cisplatin

A combination of TX and cisplatin (CDDP) increase cytotoxicity of four head and neck squamous cell carcinoma cell lines compare to either TX or CDDP (Kotowski et al., 2012), Also, low dose of TX and CDDP cause cell death and enhanced autophagy through AMPK-STAT3 pathway in head and neck cancer-initiating cells (HN–CICs) (Hu et al., 2020). They also enhance mitochondrial membrane depolarization, reduced GSH content, and down regulated MRP2 protein expression in small cell lung cancer cell lines (Zheng et al., 2013). TX with CDDP synergistically stimulate inhibition of growth of COC1 ovarian cancer cells (Zhang et al., 2009). They induce apoptosis significantly through loss of mitochondrial membrane potential, and augmented caspase-3/7 activity in human oral squamous cell carcinoma (OSCC) cells (Nakaoka et al., 2014). TX and CDDP combination suppress proliferation of MEG-A2-derived tumor *in vivo* model. They also enhance apoptosis and decreased the survival of both acquired TKI-resistant chronic myelogenous leukemia cells (CML) cells expressing mutant Bcr-Abl (Wahiduzzaman et al., 2018).

8.3. TX and vitamins

Simultaneously treatment of α-tocopheryl succinate (α-TOS) and TX in APL cells, α-TOS causes moderately antagonist of TX -induced apoptosis while α-TOS is treated after 24 h treatment of TX. α-TOS stimulates TX -induced apoptosis in NB4 cells (Freitas et al., 2009). Low dose of Vitamin D3 potentiates TX toxicity in HL = 60 cells through cytotoxicity and apoptosis via DNA laddering and raised annexin v positive cells (Rogers et al., 2014). Paricalcitol (vitamin D analogue) & TX enhance antiproliferative effect through induction of differentiation of NB-4 and HL-60 cells by apoptosis through down-regulation of Bcl-2 and Bcl-x(L) (Kumagai et al., 2005). High-dose ascorbate (ASC) and TX combination kill myeloid blasts, enhanced oxidative stress, overproduction of reactive oxygen species, and induction of apoptosis in both AML and APL cells (Noguera et al., 2017).

8.4. TX and kinases/proteosome inhibitors

MEK1 inhibitors enhance apoptosis through inhibition of extracellular signal-regulated kinases 1/2 (ERK1/2) and Bad phosphorylation in TX -treated both NB4 cells and APL primary blasts.

. It dephosphorylates Bad and inhibited the ATO-induced increased in Bcl-xL protein leading to overcome TX resistance in NB4–As(R) (Lunghi et al., 2005). MEK1 inhibitors, PD98059 and PD184352 enhance TX -induced apoptotic cell death in both NB4 and K562 cells through induction of the p53AIP1 (p53-regulated apoptosis-inducing protein 1) gene. It reduces the levels of dominant-negative (DeltaN) p73 proteins and promoted the accumulation of endogenous p73alpha through transcriptional activation and its tyrosine phosphorylation, leading to p21 up-regulation and inhibition of cells growth through cell cycle arrest, and apoptosis. *In vivo*, combination of MEK1 inhibitors and TX increase the affinity of phosphoacetylated p73 for the p53AIP1 promoter leading to p53AIP1 up-regulation and enhanced apoptosis (Lunghi et al., 2004). Gefitinib, an EGFR tyrosine kinase inhibitor combination with TX in NB4 cells are promoted expression of differentiation markers, CG11b and CD14 and ROS generation. It is required ERK pathway for enhancement of TX -induced NB4 cells differentiation (Noh et al., 2010). Combination of Gefitinib, TX, and ATRA induces myloid differentiation in APL resistant, NB4-R2 cells (de Almeida et al., 2021). Src family kinase SFK inhibitor, PP2, ATRA and TX combination enhances differentiation of NB4 cells with respect to either TX/ATRA alone or combination of both ATRA and TX together (Jung et al., 2014). Carfilzomib (CFZ), a proteasome inhibitor reduces proliferation rate of NB4 cells through c-Myc-mediated G2/M cell cycle arrest and induced apoptosis by down -regulation of expression of anti-apoptotic target genes (Zamani-Moghaddam et al., 2021). BKM120, a PI3K inhibitor enhances anti-leukemic effect of TX through down-regulation of the transcription factor, SIRT1, suppression of c-Myc leading to arrest the progression of the cell cycle progression at G1 phase in NB4 cells (Bashash et al., 2018).

9. Conclusion

TX is single drug used for treatment of all age group of APL patients to complete remission for longer time. Recently it has been reported resistant to APL patients having other fusion gene (PLZF-RARα). To overcome of TX resistant, we will need to investigate new target/mechanism of its action through further research works or find other drugs/inhibitors/vitamins that enhanced toxicity of TX in APL cells. TX works inside APL patients diverse mechanism, This review summaries updated mechanism of action of TX alone and its combination with other drugs/inhibitors/vitamins in leukemia cells. It provides researcher updated knowledge of TX mode of action and helped to continued further research in APL pathophysiology to discover new anti-leukemic drugs.

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Contribution

SK – develop concept & idea, wrote manuscript, made diagram; Ananta & SB – wrote manuscript.

CRediT authorship contribution statement

Ananta: significantly contributed in writing and figure design. **Swati Benerjee:** wrote some portion of manuscript. **Paul B. Tchounwou:** Read and given valuable inputs and suggestion. **Sanjay Kumar:** conceptual design manuscript, revised, and mostly wrote manuscript.

Declaration of competing interest

The authors declare that they have no competing financial interests.

Data availability

The data that has been used is confidential.

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