Pharmacological combination for leukemia treatment.

KEYWORDS

- ❑ TARGETED DRUGS
- ❑ ACUTE MYELOID LEUKEMIA
- ❑ AML FLT3-ITD+
- ❑ TARGETED THERAPY
- ❑ CELLULAR STRESS
- ❑ PROTEOSTATIC STRESS
- ❑ OXIDATIVE STRESS

AREA

- ❑ PHARMACEUTICAL

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Patent Type
Patent for invention.

Ownership
Sapienza Università di Roma 100%.

Inventors
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Industrial & Commercial Reference
Pharmaceutical companies.

Time to Market
TRL-4: The drug combination has been successfully tested *in vitro* on AML cell lines and *ex-vivo* on primary cells isolated from patients. Preliminary experiments *in vivo* do not show general toxicity in wt murine models.

Availability
Licensing, Research, Develop-ment, Experimentation and Collaboration.

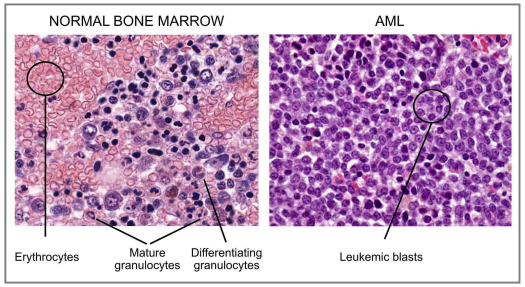

Fig. 1 The bone marrow is the site of hemopoiesis, that is production and differentiation of blood cells. In a bone marrow biopsy specimen it is possible to identify the blood cell precursors at different stages of differentiation, like for example erythrocytes and granulocytes (as shown in the left panel). On the contrary, an AML affected bone marrow is populated almost exclusively by leukemic blasts, up to 90% (as shown in the right panel).

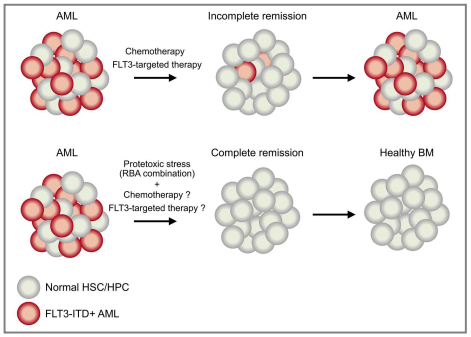

Fig. 2 The present therapy for FLT3-ITD+ AML, based on chemotherapy with or without specific FLT3 inhibitors, is not able to eliminate the leukemic stem cells. Indeed different clinical trials showed incomplete remission and insurgence of resistance. The combination of all trans retinoic acid (R), bortezomib (B) and arsenic trioxide (A), inducing proteotoxic stress, could lead to leukemic stem cell death, eradicating the disease.

Abstract
The invention proposes to use a combination of three drugs (All-Trans-Retinoic-Acid, Arsenic Trioxide and Bortezomib) to treat FLT3-ITD positive Acute Myeloid Leukemia (AML), on the basis of experimental results obtained *in vitro* on AML cell lines and on primary cells isolated from AML patient bearing the FLT3-ITD mutation. The main advantage provided by the combination is the possibility to use very low amounts of each drugs, which confers high efficacy on target cells but low general toxicity, as demonstrated by *in vitro* experiments on hematopoietic progenitors isolated from healthy donors and by *in vivo* experiments on wt mice.

Pubblicazioni

- ❖ Masciarelli S*, Capuano E, Ottone T, Divona M, Lavorgna S, Liccardo F, Śniegocka M, Travaglini S, Noguera NI, Picardi A, Petrozza V, Fatica A, Tamagnone L, Voso MT, Lo Coco F, Fazi F. Retinoic acid synergizes with the unfolded protein response and oxidative stress to induce cell death in FLT3-ITD+ AML. Blood Adv. 2019 Dec 23;3(24):4155-4160. doi: 10.1182/bloodadvances.2019000540.

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Technical Description

FLT3-ITD mutation causes cell protein homeostasis (proteostasis) alteration. Indeed this protein cannot be properly folded hence it accumulates in the endoplasmic reticulum causing a basal low level of stress to which leukemic cells are adapted. *In vitro* experiments with AML cell lines, primary cells isolated from FLT3-ITD+ patients and normal hematopoietic progenitors obtained by healthy donors, demonstrated that the combination of all-trans Retinoic Acid, Arsenic Trioxide e Bortezomib, used at low doses not harmful when each drug is used as single agent, causes levels of proteostatic and oxidative stresses resulting highly toxic for FLT3-ITD AML cells but not for healthy progenitors with a normal proteostatic balance.

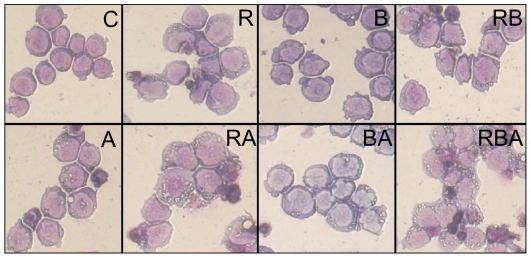

Fig. 3 FLT-3+ AML cells are sensitive to the triple combination RBA as shown by cell death observed at optical microscope after Wright-Giemsa staining.

Technologies & Advantages

ITD mutation in the tyrosin kinase receptor FLT-3 (FLT3- ITD) has a frequency of 30% in AML, leading to a negative prognosis. Various clinical trials with different tyrosine kinase inhibitors resulted in incomplete responses and showed insurgency of resistance. Furthermore, different strategies have been developed to target FLT3-ITD, based on its structural defects or on aberrantly activated signaling pathways. Nonetheless, these use high doses of drugs that are likely to cause off target effects. On the contrary, the proposed combination utilizes low doses of each drug, such that they are not harmful when they are used as single agents. It is likely that this combination will show high specificity, since, because of the mutation, the target cells are particularly sensitive to the stresses generated by the combination, with a low general toxicity. Furthermore the proposed drugs have been approved by regulatory agencies, although with other indications and not in combination, rendering the development of pre-clinical and clinical trials faster.

Applications

The proposed combination of three drugs, All Trans Retinoic Acid (ATRA), Arsenic Trioxide (ATO) and Bortezomib (Btz), is of interest for the field of clinical oncology and hematology. It is aimed to the treatment of Acute Myeloid Leukemia positive for the mutation FLT3-ITD (FLT3-ITD+ AML). The current therapeutic strategies for FLT3-ITD+ AML show incomplete responses with frequent insurgency of resistance. The three drugs proposed in combination are approved by regulatory agencies for leukemia and/or for multiple myeloma. In particular the combination of ATRA and ATO are indicated for acute promyelocytic leukemia while Btz is indicated for multiple myeloma. The triple combination of the drugs has never been tested. After further investigations it could have a significant impact in clinical treatment of FLT3-ITD+ AML.

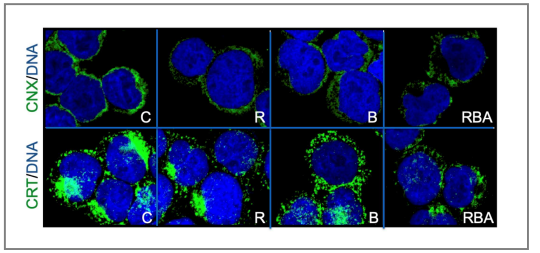

Fig. 4 The combination of all trans retinoic acid (R), bortezomib (B) and arsenic trioxide (A) dramatically alters the morphology of the endoplasmic reticulum, the organelle of the cell that is devoted to the production of the proteins embedded in cell membranes or secreted. The endoplasmic reticulum is stained in green while the nucleus of the cell is stained in blue.

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