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VALUTAZIONE DELLA MALATTIA MINIMA RESIDUA IN PAZIENTI AFFETTI DA LEUCEMIA MIELOIDE ACUTA IN TRATTAMENTO CON AGENTI IPOMETILANTI E VENETOCLAX

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Nuovi Endopint ed Outcome clinici per predire la risposta terapeutica nelle Neoplasie Ematologiche: Venetoclax e valutazione MRD

Sommario

Abstract

Acute myeloid leukemia (AML) is a genetically heterogeneous malignant clonal disorder of the hematopoietic system that is characterized by uncontrolled proliferation of immature, abnormal blast cells and impaired production of normal blood cells. The therapy of young adults is based on intensive chemotherapy. Treatment of older patients with AML is quite challenging, an older age is independently associated with an inferior outcome. Hypomethylating agents such as 5-azacytidine and decitabine, has shown to be a promising option for older patients with AML, who are not suitable candidates for intensive therapies. Both drugs showed a survival advantage compared with conventional therapy approaches in older patients with AML. Several other treatments with the addition of novel agents are currently under investigation.

Venetoclax (VEN) is an oral, potent, and selective BCL2 inhibitor, FDA approved in 2016 for the treatment of patients with chronic lymphocytic leukemia (CLL) and 17p deletion. As a single agent for patients with Relapsed/Refractory (R/R) AML, VEN has demonstrated clinical activity, although responses were relatively modest and short-lived. Synergistic activity against myeloid malignancies is seen in vitro and in vivo with VEN in combination with lower intensity antileukemia therapy, such as low-dose cytarabine (LDAC) or hypomethylating agents (HMA) (i.e., azacitidine or decitabine). Clinical data are now also available, demonstrating encouraging safety and efficacy in treatment-naive elderly and/or unfit AML patients, with VEN in combination with either LDAC (NCT02287233), or the HMAs azacitidine or decitabine (NCT02203773), leading to FDA breakthrough designations for these treatment combinations

This project, aims to analyze the response of AML patients to new drugs, in particular to Venetoclax.

We will collect data on consecutive patients affected by de novo or secondary AML according to WHO 2016 criteria, in relapse or refractory phase of disease. Data will include clinical data and response data (minimal residual disease tested by multiparameter flow cytometry or MFC).

The primary endpoint of the project will be: percentage of response to reinduction therapy and time to reach response and deep of response.

The Secondary clinical endpoints will be: Therapy-related Mortality, Early Relapse Rate, Identification of risk factors for resistance to the therapy. Overall Survivall and Disease Free Survival. The secondary biological endpoints will be: Incidence of most common

mutation (FLT3, NPM1, CEBPA, DNMT3A, ASXL1, IDH1, IDH2, TP53).

All of these data could allow to identify early markers of response to the therapies. Accurate knowledge of the biological characteristics of the disease could allow a personal approach to therapy, avoiding toxicity from inappropriate therapeutic strategies.

Background

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by uncontrolled proliferation and accumulation of immature myeloid precursor cells in the bone marrow leading to impaired hematopoiesis and bone marrow failure [1]. It is the most common acute leukemia in adults with an incidence of up to 17 per 100,000 per year in patients older than 65 years [2]. [PROGNOSI: 2.4% patients stay alive and DFS 10 after diagnosi[MA1]] AML is a clonal disease caused by genetic mutations in normal myeloid hematopoetic progenitor cells, leading to altered self-renewal, differentiation and proliferation [1].

Genomic Landscape of Acute Genomic Leukemia

Cytogenetic and sequencing analyses have revealed at least 11 genetic classes of AML3 and over 20 subsets can be assigned when also considering cell differentiation states of the leukemic blasts4,5 . Deep sequencing of AML by The Cancer Genome Atlas (TCGA) revealed a heterogeneous disease with nearly 2,000 somatically mutated genes observed across 200 patients 6 . Many of the recurrent cytogenetic events and somatic mutations have been shown to carry prognostic significance3,7,8

A small number of therapies targeted to mutational events have been developed for AML patients, with the current standard of care largely unchanged over the past 30–40 years. The first targeted therapy for AML involved use of all-trans retinoic acid (ATRA) in combination with arsenic trioxide for patients with rearrangement of the retinoic acid receptor16,17. More recently, fms related tyrosine kinase 3 (FLT3) inhibitors have been developed for FLT3 mutational events that occur in ~20–30% of AML patients18–21. FLT3 inhibitors deployed as single agents yielded responses of only 2–6 months22–25. Midostaurin, a broad-spectrum FLT3 inhibitor, was recently approved for use in newly diagnosed, FLT3-mutated AML patients in combination with standard of care chemotherapy 26; however, relapse was still prevalent in this setting. Targeting of mutant isocitrate dehydrogenase (NADP(+)) 1, cytosolic 1/2 (IDH1/2)27, has shown clinical benefit leading to approval of the IDH2 inhibitor, enasidenib, and the IDH1 inhibitor, ivosidenib28,29. Additional proposed strategies have included inhibition of epigenetic modifiers such as enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2)30, LSD1 zinc finger family protein (LSD1)31, and DOT1L like histone lysine methyltransferase (DOT1L)32 based on direct mutation of these targets or synthetic lethality in the context of drug combinations (ATRA and LSD1 inhibitors) or specific genetic features (lysine methyltransferase 2A (KMT2A)-gene rearrangement for DOT1L

inhibitors). Hypomethylating agents have been employed in AML patients with better responses reported for certain genetic subsets, such as those with mutation of TET233 or tumor protein 53 (TP53)34. Most recently, the BCL2 apoptosis regulator (BCL2) inhibitor, venetoclax, showed a ~20% response rate when used as a single agent in relapsed patients35 with higher response rates (~60%) reported in combination with hypomethylating agents in newly diagnosed, elderly AML patients36

Standard of care for Acute Myeloid Leukemia

Intensive chemotherapy is the gold –standard for fit patients; the most USED schedule is anthacycline-Cytarabine based regimen…… [AGGIUNGI TASSI DI RISPOSTA, LINEE GUIDA NCCN, ELN].

Lower-intensity therapies, including the hypomethylating agents (HMA) azacitidine and decitabine, have been the mainstay of therapy for older AML patients who are poor candidates for intensive induction chemotherapy. HMA monotherapy is associated with complete remission (CR) plus CR with incomplete count recovery (CRi) rates of ~15–30%, median time to response ranging from 3 to 4 months, median overall survival (OS) of <12 months, and a generally tolerable safety profile in the older AML population [polleya et al, Leukemia 2019, vd poi biblio]

Bcl2 and Apoptosis

B-cell lymphoma 2 (BCL-2) is an antiapoptotic protein that plays key roles in the survival and therapeutic resistance of AML cells, including the leukemia stem cell (LSC) population [8, 9]. BCL-2 and its family members prevent apoptosis by binding to and sequestering pro-apoptotic proteins [1[MA2]0].

Venetoclax

Venetoclax is a potent, selective, oral inhibitor of BCL-2 which, in preclinical studies, demonstrated anti-AML and anti-LSC activity as a monotherapy and additive properties with azacitidine, including the ability to target LSCs through disruption of energy metabolism [8, 9, 11, 12].

Mechanism of action

Venetoclax in AML: clinical studies and results

Ventoclax come agente singolo

In patients with relapsed and refractory (R/R) AML, venetoclax had modest single-agent activity (19% CR/CRi) [13]. In contrast, venetoclax 400 mg in combination with either azacitidine or decitabine demonstrated significant activity in the up-front treatment setting, with a CR/ CRi rate of 71% and 74%, median duration of response of 21.2 and 15.0

months, and median OS of 16.9 and 16.2 months, for azacitidine and decitabine, respectively [14]. Efficacy was observed among all AML subgroups, including patients with secondary AML, those with adverse-risk cytogenetics, and across the genomic landscape of the disease [15]. In a separate study, venetoclax was also shown to be safe and effective in combination with low-dose cytarabine (LDAC) [16].
Venetoclax e HMA in R/R AML
CITOPENIA ASSOCIATA AL TRATTAMENTO

Methods

Patients

Inclusion and Exclusion Criteria

Study design and Therapy

Haematological Monitoring and Response Assessment

Minimal Residual Disease (MRD) Monitoring

Statistical Methods

Results

Patients characteristics

Cytogenetic and Molecular baseline characteristics

Treatment Responses and Survival

MRD Responses

Treatment Adherence, Discontinuation, Safety and Tolerability
TREATMENT ASSOCIATED CYTOPENIA:

Discussion

Haematological responses and survival outcomes
L'aggiunta successiva di venetoclax ad un trattamento già in corso con HMA in pazienti che dimostrino un aumento della MRD è un argomento di nuova concezione e che necessita comunque di ulteriore approfondimento

La prosecuzione del trattamento è ancora argomento di discussione e molti trial sono in corso di valutazione
La citopenia associata al trattamento: il managment

Biological Explanation for Venetoclax Efficacy

MRD

Conclusion

Nonostante il numero esiguo di pazienti questi studio ha evidenziato la risposta in termini di MRD e possibilità di trapianto allogenico concessa a pazienti R/R chemorefrattari
La ricorrenza di citopenia associata al trattamento e la presenza di diverse indicazioni in letteratura hanno portato a redigere un documento sulla gestione di tale eventualità, condivisa dall'unità operativa di ematologia

Bibliography

1. Papaemmanuil, E.; Gerstung, M.; Bullinger, L.; Gaidzik, V.I.; Paschka, P.; Roberts, N.D.; Potter, N.E.; Heuser, M.; Thol, F.; Bolli, N.; et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. N. Engl. J. Med. 2016, 374, 2209–2221.
2. Cancer Genome Atlas Research Network; Ley, T.J.; Miller, C.; Ding, L.; Raphael, B.J.; Mungall, A.J.; Robertson, A.G.; Hoadley, K.; Triche, T.J.; Laird, P.W.; et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N. Engl. J. Med. 2013, 368, 2059–2074.