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PhD Thesis

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Myelodysplastic Neoplasms and the Before and Beyond

Exploring Prognostic Factors and the Therapeutic Role of Vitamin C in Myeloid Malignancies

Principal Supervisor: Professor Kirsten Grønbæk

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Resumé

Myelodysplastiske neoplasmer (MDS) er myeloide kræftsygdomme, som opstår i knoglemarvens stamceller og forårsager varierende grader af knoglemarvssvigt. Sygdommen er karakteriseret ved blodmangel og en risiko for videreudvikling til akut myeloid leukæmi. I de fleste tilfælde skyldes MDS en opstået genfejl (mutation), som giver ophav til klonal blodcelledannelse. Mutationer relateret til MDS kan også være til stede hos patienter med uforklaret blodmangel, som ikke har synlige forandringer i knoglemarven. I dette tilfælde kaldes tilstanden på engelsk clonal cytopenia of undetermined significance (CCUS), som er et forstadium til MDS. Faktorer af betydning for videreudvikling til MDS er mangelfuldt belyst, og der findes endnu ingen forebyggende behandling. Når MDS først er opstået, er den eneste helbredende behandling knoglemarvstransplantation, som ikke kan tilbydes ældre patienter. Eftersom MDS primært er en sygdom hos ældre, behandles de fleste patienter med høj-risiko MDS med såkaldt epigenetisk modificerende lægemidler (oftest azacitidin). Halvdelen har dog ikke effekt af behandlingen.
Med de fire studier, som er inkluderet i denne ph.d.-afhandling, forsøgte vi at imødegå behovene for bedre identifikation af patienter med CCUS i risiko for udvikling til MDS og forebyggende behandling samt en sikker, mere effektiv behandling hos ældre patienter med høj-risiko MDS.
I studie I viste vi, at submikroskopiske kromosomale forandringer var til stede i blodcellerne hos visse patienter med CCUS og var associeret med en dårligere overlevelse. Undersøgelse for sådanne forandringer er dog ikke en del af den kliniske udredning af disse patienter.
Studie II var et litteraturstudie af C-vitamins rolle i epigenetisk kræftbehandling. Adskillige cellestudier, museforsøg og et begrænset antal kliniske studier understøtter et biologisk rationale for en eventuel terapeutisk effekt af C-vitamin i myeloid blodkræft. Der mangler dog evidens fra højkvalitets lodtrækningsforsøg med patienter (randomiserede, kontrollerede studier; RCT).
Vi opstartede derfor to fase 2 RCT med oralt C-vitamin som kosttilskud hos patienter med CCUS eller lav-risiko myeloide kræftsygdomme (studie III), og hos patienter med høj-risiko myeloide kræftsygdomme som kombinationsbehandling med azacitidin (studie IV). Begge studier er i gang, men en blindet foreløbig analyse (en såkaldt interimanalyse) blev udført af studie III. Der var ikke nogen forskel de to behandlingsgrupper imellem i hyppighed af respons eller sygdomsforværring, men en længere overlevelse blev observeret i den behandlingsarm, hvor vi iagttog en stigning af C-vitamin-koncentrationen i blodets væskefase. Det kunne ikke udelukkes, at en tilfældig ulige fordeling af kliniske faktorer af betydning for sygdomsforløbet påvirkede de foreløbige resultater, men hvis effekten også er til stede i den endelige analyse, bør det give anledning til undersøgelse i et større RCT.

Summary

Myelodysplastic neoplasms (MDS) are myeloid cancers originating in the hematopoietic stem cells (HSCs) in the bone marrow that cause varying degrees of hematopoietic failure. It is characterized by peripheral blood cytopenia and an increased risk of progression to acute myeloid leukemia. The initiating event is in most cases an acquired mutation in the HSCs which gives rise to clonal hematopoiesis. Somatic mutations in genes recurrently affected in MDS can also be detected in patients (pts) with unexplained cytopenia and no morphological evidence of MDS; a condition referred to as clonal cytopenia of undetermined significance (CCUS). CCUS is a precursor condition of MDS, but the natural history shows significant variability and factors of prognostic relevance are only beginning to be elucidated. Pts with CCUS are often followed with watchful waiting for years as no known prevention exists. When MDS develop, the only curative therapy is allogeneic stem cell transplantation which is not eligible in older pts with comorbidity. Thus, first-line therapy in most pts with higher-risk (HR) MDS is the epigenetically modifying drugs, hypomethylating agents (HMA), but half of pts are resistant to HMA.

With the four studies included in this thesis, we approached these unmet needs in identification of CCUS pts at risk of progression and prevention, and of safe, effective therapies for unfit HR pts.

In study I, we showed for the first time that submicroscopic chromosomal aberrations could be detected in the hematopoietic cells in a subset of pts with CCUS identifying pts with a higher risk of mortality. However, such analysis is not part of the diagnostic evaluation of these pts.

In study II, we reviewed the literature on vitamin C in epigenetic cancer therapy. Multiple *in vitro*, murine, and a limited number of clinical studies have provided a biological rationale for a therapeutic role of vitamin C both in the prevention of progression of low-risk (LR) myeloid malignancies and in combination therapy with HMA in HR pts. However, evidence from high-quality randomized, controlled trials (RCTs) remains to be presented.

To bridge this gap, we conducted two phase 2 RCTs of oral vitamin C supplementation as single agent in pts with CCUS or LR myeloid malignancies (study III), and in pts with HR myeloid malignancies as add-on therapy to HMA (study IV). Both studies are ongoing but enrolment is complete in study III, and a total of 84 pts had completed study treatment and were included in a blinded interim analysis. While no difference between treatment arms was observed in rates of hematological responses or disease progression during study treatment, survival was significantly longer in the treatment arm with an elevation of plasma vitamin C levels. It could not be ruled out that an unbalanced randomization of baseline characteristics impacted the results but if the effect persists in the final analysis, this warrants further investigation in a larger RCT.