Press release

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Basic information

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Department of: Clinical Medicine

Main supervisor: Birgitte Klug Albertsen

Title of dissertation: Asparaginase treatment in childhood acute lymphoblastic leukemia - outcome and side effects

Date for defence: 4/10-2019 at (time of day): 14:00 Place: Auditorium J116-113, level 1, entreance J, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N.

Press release (Danish)

Vigtigheden af asparaginase i behandlingen af akut lymfatisk leukæmi hos børn

Akut lymfatisk leukæmi er den hyppigste kræftsygdom hos børn. Behandlingen er kompleks og består af mange forskellige typer af kemoterapi herunder asparaginase. Asparaginase er et enzym som omdanner den ikke-essentielle aminosyre asparagin til aspartat, hvorved asparagin fjernes fra blodet. I modsætning til de normale celler kan leukæmicellerne ikke gendanne asparagin, og de dør derfor af denne behandling. Virkningen af asparaginase kan måles som asparaginase enzymaktivitet i patientens blod. Desværre er der en del børn der oplever bivirkninger til asparaginase, og som derfor er nødt til at afkorte behandlingen med dette stof.
Vi undersøgte konsekvensen for de patienter der fik en afkortet asparaginase behandling og fandt at de, som fik afkortet deres asparaginase behandling eller ikke havde nogen målbar asparaginase enzymaktivitet, havde en signifikant øget risiko for tilbagefald. Denne sammenhæng kunne kun påvises ved at inddrage enzymaktivitetsmålinger i analyserne. Resultaterne understreger vigtigheden af at måle asparaginase enzymaktivitet for at identificere patienter uden aktivitet og derefter ændre behandling ved at give en anden type asparaginase.
Den hyppigste bivirkning til asparaginase behandlingen er allergi. Vi undersøgte om patienter med allergi var genetisk disponeret til denne bivirkning ved at lave en genetisk sammenligning. Vi fandt en association mellem en genetisk variation i relation til CNOT3-genet og asparaginase allergi. Denne sammenhæng opstod, da vi brugte enzymaktivitetsmålingerne til at differentiere mellem ”sande” allergier overfor asparaginase og reaktioner, som blot lignede.
Asparaginase påvirker kroppens normale protein syntese og dermed også koagulationssystemet, hvilket resulterer i en øget risiko for at patienterne danner blodpropper. Vi undersøgte sammenhængen mellem asparaginase enzymaktivitet og en lang række koagulations parametre. Vi fandt en negativ sammenhæng mellem antitrombin og enzymaktiviteter mellem 0 og 250 IU/L, men ikke ved enzymaktiviteter højere end 250 IU/L. Fibrinogen viste tilsvarende korrelation. Dermed ville dosis justering ikke medføre mindre påvirkning af disse parametre.
Samlet set understreger resultaterne af dette PhD projekt vigtigheden i at måle asparaginase enzymaktivitet for at sikre optimal effekt af stoffet, da en afkortet behandling resulterer i en øget risiko for tilbagefald. Studiet er et nyt ph.d.-projekt fra Aarhus Universitet, Health. Projektet er gennemført af Sofie Gottschalk Højfeldt, der forsvarer det d. 4/10-2019

Forsvaret af ph.d.-projektet er offentligt og finder sted den 4/10-2019 kl. 14:00 i auditorium J116-113, Aarhus Universitets Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N. Titlen på projektet er ”Asparaginase treatment in childhood acute lymphoblastic leukemia - outcome and side effects”. Yderligere oplysninger: Ph.d.-studerende Sofie Gottschalk Højfeldt, e-mail: sofihj@rm.dk, tlf. 51218689.

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Press release (English)

The importance of asparaginase in the treatment of acute lymphoblastic leukemia in children

The most common type of childhood cancer is acute lymphoblastic leukemia. The treatment is complex and consists of several different types of chemotherapeutic drugs. Asparaginase is a widely used drug in ALL therapy. It is an enzyme that catalyzes the non-essential amino acid asparagine into aspartic acid and thereby depletes the blood of asparagine. Unlike normal cells, leukemic cells do not have the capacity to re-synthesize asparagine and thus they undergo apoptosis. The efficacy of asparaginase can be measured as asparaginase enzyme activity in at blood sample. Unfortunately some children must truncate the treatment of asparaginase due to side effects.
We investigated the consequence of truncated asparaginase treatment and found that patients with truncated asparaginase treatment or no measurable asparaginase enzyme activity had a significantly increased risk of relapse. This association was only found when asparaginase enzyme activity measurements were included in the analysis. Our results emphasized the importance of using these measurements in order to identify patients without enzyme activity and change their asparaginase preparation.
The most frequent toxicity to asparaginase is allergy. We investigated if patients were genetically predisposed to this toxicity by doing a genetic comparison. We found that a variation in the CNOT3 locus on chromosome 19 was associated with asparaginase allergy. The association was found when we included asparaginase enzyme activity measurements to differentiate between “true” allergic reactions to asparaginase and “allergy-like” reactions.
Asparaginase affects the body's protein synthesis and thereby also the coagulation system. Patients thus have an increased risk of thromboembolisms. We investigated the correlation between asparaginase enzyme activity and several different coagulation parameters. We found a negative correlation between antithrombin and AEA levels between 0 and 250 IU/L, but no correlation for enzyme activity levels above 250 IU/L. Fibrinogen showed similar correlation. Thus, dosing adjustments would not result in less affected values.
In conclusion the results of this PhD project emphasizes the importance of measuring asparaginase enzyme activity in order to ensure optimal efficacy of the drug, since truncation of asparaginase leads to an increased risk of relapse. The project was carried out by Sofie Gottschalk Højfeldt, who is defending her dissertation on 4/10-2019.

The defence is public and takes place on 4/10-2019 at 14:00 in auditorium J116-113, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N. The title of the project is ”Asparaginase treatment in childhood acute lymphoblastic leukemia - outcome and side effects”. For more information, please contact PhD student Sofie Gottschalk Højfeldt, email: sofihj@rm.dk, Phone +45 51218689.

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