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Impact of Toll-like receptor (TLR2 and TLR4) polymorphisms on infectious complications in patients with acute myeloid leukemia

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INTRODUCTION

Infectious complications continue to be one of the major causes of morbidity and mortality in patients with acute myeloid leukemia (AML).

Toll-like receptors (TLR) form a group of functionally important pattern-recognition receptors of innate immunity.

Several single nucleotide polymorphisms (SNPs) of TLRs can affect genetic susceptibility to infections or even sepsis.

METHODS

We sought to investigate the impact of different SNPs of TLR2 (Arg753Gln) and TLR4 (Asp299Gly and Thr399Ile) on the incidence of infections in 156 patients with newly diagnosed AML following induction chemotherapy (cytarabine combined with idarubicine or mitoxantrone).

The incidences of neutropenic fever, pneumonia, and sepsis were assessed. Detection of TLR SNPs were performed by pyrosequencing and revealed that 10 patients (6.4%) had the TLR2 polymorphism and 20 of 156 patients (12.8%) were tested positive for TLR4 SNPs.

RESULTS

Patients carrying the TLR2 SNP or co-segregating TLR4 polymorphisms (n=19) had a higher risk for both sepsis and pneumonia while there was no correlation concerning the number of fever episodes or the duration of neutropenic fever. Importantly, patients harboring both TLR4 polymorphisms had a significant higher risk of sepsis after induction chemotherapy (OR 3.5, 95% CI 1.19-10.22, *p=0.026*). Furthermore, the presence of the TLR2 Arg753Gln polymorphism was associated with a significant increase of pneumonia in AML patients (OR 9.3, 95% CI 1.89-45.44, *p=0.003)*

Table 1: Patient characteristics of a cohort of 156 patients with acute myeloid leukemia who underwent induction chemotherapy and were included in the study.

	n=156
Median age, y (range)	56.5 (19-78)
Male sex, no (%)	75 (48.1)
Type of acute myeloid leukemia	
de novo (%)	102 (65.4)
Secondary, therapy associated (%)	54 (34.6)
Cytogenetic risk group	
Low (%)	20 (12.8)
Intermediate (%)	88 (56.4)
Poor (%)	44 (28.2)
n.d.	4 (2.6)
WBC count at diagnosis (/nl), median (range)	16.5 (0.3-330)
Platelet count at diagnosis (/nl), median (range)	46 (2-332)
Hemoglobin level at diagnosis (mmol/l), median (range)	5.65 (2.5-8.8)
Peripheral blood blasts (%), median (range)	28 (0-95)
Bone marrow blasts (%), median (range)	74.5 (17-98)
Outcome after induction chemotherapy	
Alive	153
Dead	3

Table 2: Association of TLR polymorphism with sepsis in patients with acute myeloid leukemia undergoing induction chemotherapy.

Genetic ariable	No sepsis (%)	Sepsis (%)	Odds ratio (95% CI)	*P* value
TLR2 wild type	79 (54.1%)	67 (45.9%)	4.7 (0.97 – 22.97)	*0.05*
TLR2 Arg753Gln	2 (20%)	8 (80%)		
TLR4 wild type	76 (55.5%)	61 (44.5%)	3.5 (1.19 – 10.22)	*0.026*
TLR4 SNPs	5 (26.3%)	14 (73.7%)		

Table 3: Association of TLR polymorphism with pneumonia In patients with acute myeloid leukemia undergoing induction chemotherapy.

Genetic variable	No Pneumonia (%)	Pneumonia (%)	Odds ratio (95% CI)	*P* value
TLR2 wild type	102 (69.9%)	44 (30.1%)	9.3 (1.89 – 45.44)	*0.003*
TLR2 Arg753Gln	2 (20%)	8 (80%)		
TLR4 wild type	96 (70.1%)	41 (29.9%)	3.2 (1.27 – 8.59)	*0.020*
TLR4 SNPs	8 (42.1%)	11 (57.9%)		

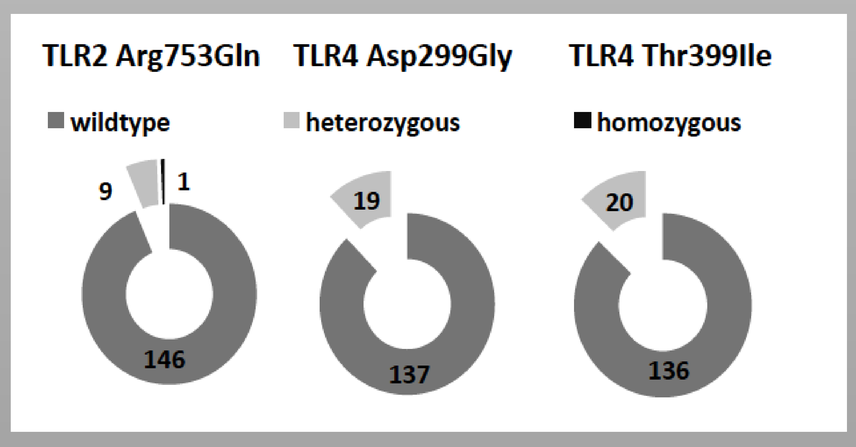

Figure 1

Allel frequency of each TLR polymorphism (TLR2 Arg753Gln, TLR4 Asp299Gly and Thr399Ile). 19 patients were heterozygous for both TLR4 SNPs, one patient was positive for TLR4 Thr399Ile only.

CONCLUSION

To our best knowledge, this study represents the first analysis demonstrating that polymorphisms of the innate immune system influence the risk of serious infections in patients with AML undergoing induction chemotherapy.

1. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nature immunology **2010**; 11(5): 373-84.
2. Kumpf O, Giamarellos-Bourboulis EJ, Koch A, et al. Influence of genetic variations in TLR4 and TIRAP/Mal on the course of sepsis and pneumonia and cytokine release: an observational study in three cohorts. Critical care (London, England) **2010**; 14(3): R103.
2. Yomade O, Spies-Weisshart B, Glaser A, Schnetzke U, Hochhaus A, Scholl S. Impact of NOD2 polymorphisms on infectious complications following chemotherapy in patients with acute myeloid leukaemia. Annals of hematology **2013**.
3. Nachtigall I, Tamarkin A, Tafelski S, et al. Polymorphisms of the toll-like receptor 2 and 4 genes are associated with faster progression and a more severe course of sepsis in critically ill patients. The Journal of international medical research **2014**; 42(1): 93-110.
4. Papadopoulos AI, Ferwerda B, Antoniadou A, et al. Association of toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms with increased infection risk in patients with advanced HIV-1 infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2010**; 51(2): 242-7.

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