

Anakinra to reduce fever during neutropenia in autologous stem cell transplantation recipients with mucositis: first report of the AFFECT-2 study.

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INTRODUCTION

High-dose chemotherapy and stem cell transplantation (SCT) is often complicated by fever during neutropenia (FN). In majority, no microbial infection can be detected.¹ Our hypothesis is that chemotherapy-induced mucositis causes IL-1 mediated local and systemic inflammation contributing to FN.^{2,3} Recombinant human IL-1 receptor

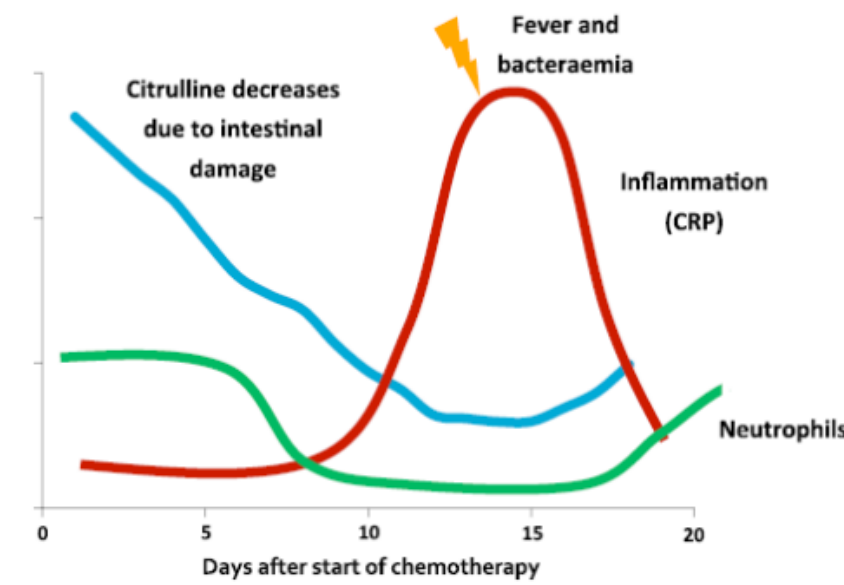
antagonist anakinra is effective in ameliorating melphalan-induced mucositis in rats.⁴

Figure 1. Relationship between FN and mucositis in patients receiving high-dose chemotherapy.

Plasma citrulline is a marker of functional enterocyte mass.

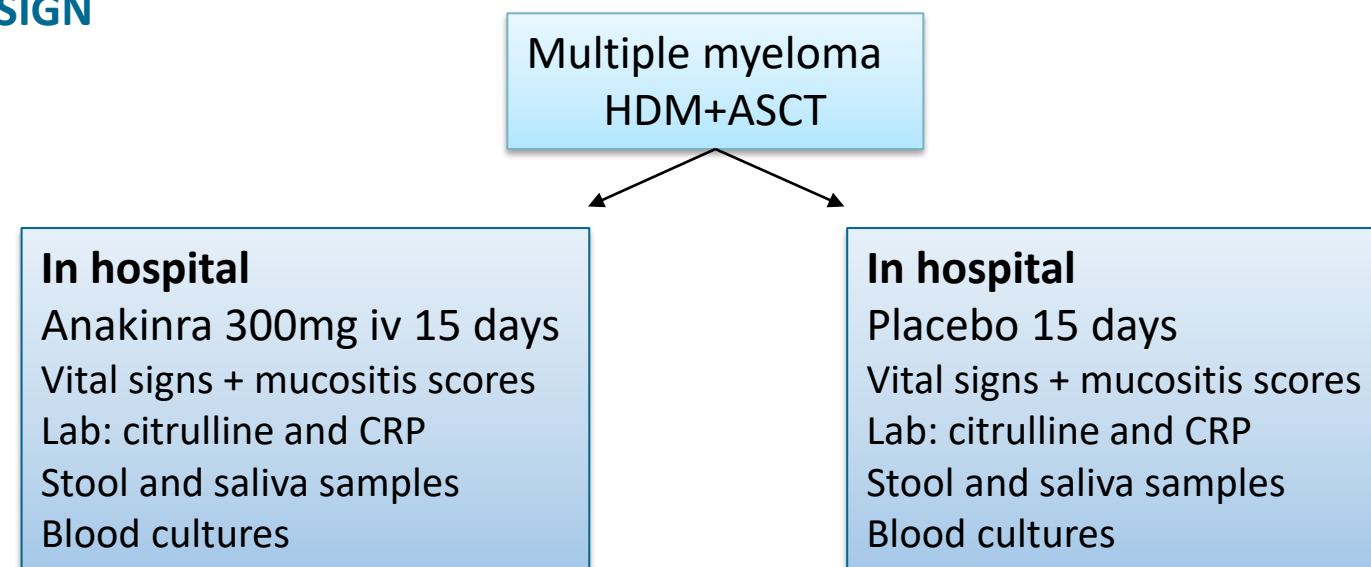
Citrulline <10 umol/L reflects severe gut mucositis. Serum CRP represents systemic inflammation as acute phase protein.

Adapted from van der Velden et al. 2014.



In this two-center phase 2 trial, multiple myeloma (MM) patients receiving high-dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT) were randomized between placebo or IL-1 receptor antagonist anakinra to reduce the incidence of fever during neutropenia (FN) and mucositis severity (Clinicaltrials.gov NCT04099901).

TRIAL DESIGN



Sample size: 90 patients were required to detect a reduction from 80% to 50% in our primary outcome incidence of FN, with a two-sided test, an α of 0,05 and a power of 80%.

FN definition: tympanic temperature $\geq 38,5^{\circ}\text{C}$ and an absolute neutrophil count $< 0,5 \times 10^9 /\text{l}$ or expected to fall below $0,5 \times 10^9 /\text{l}$ in the next 48 hours.

RESULTS

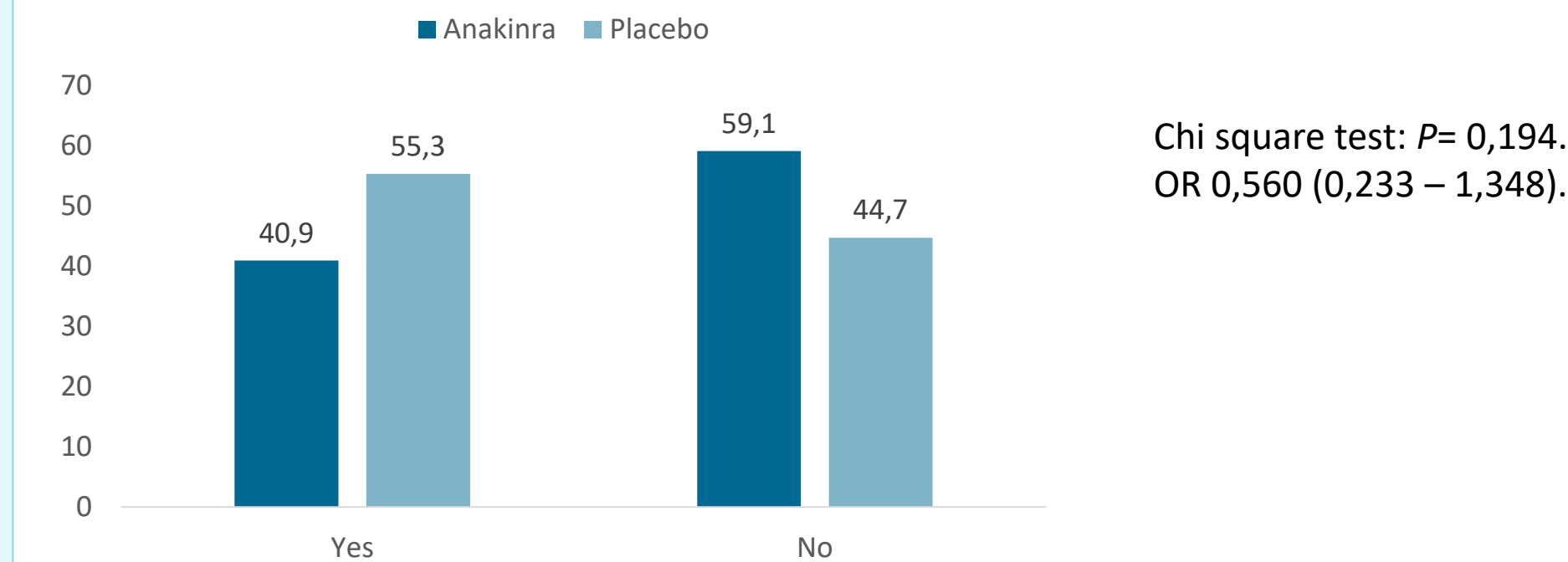
Patients were included between 2019 and March 2023. 88 patients enrolled and randomized. ITT population consisted of 82 patients who received ≥ 1 dose of study medication.

BASIC CHARACTERISTICS

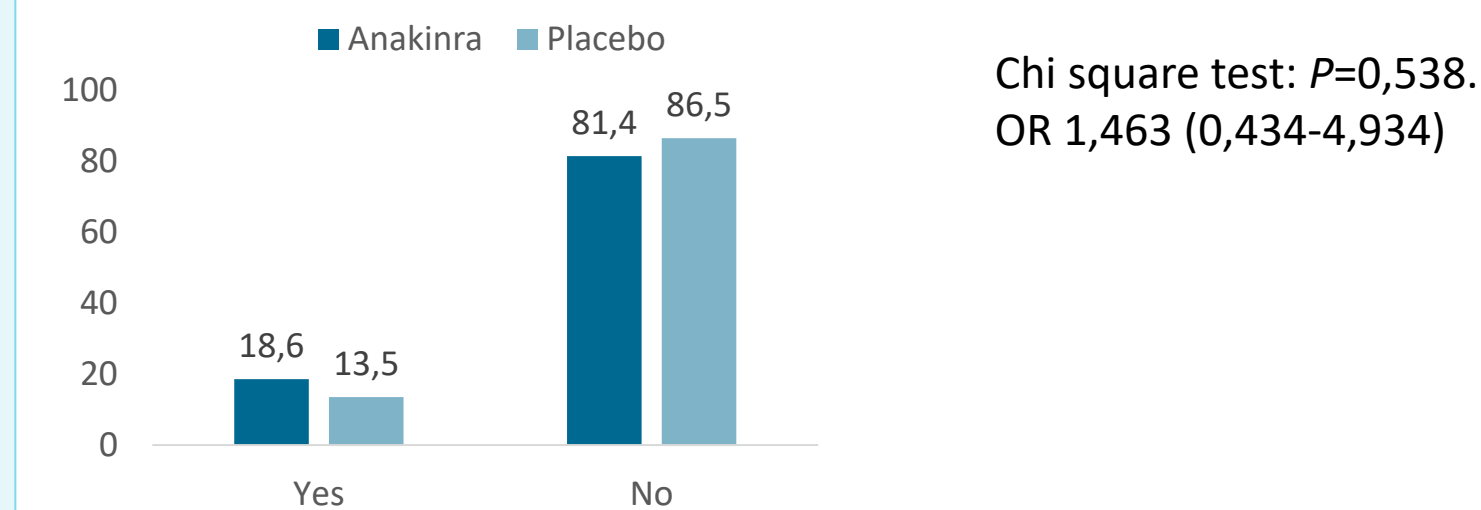
Table 1. Basic characteristics of ITT population

	Anakinra	Placebo
Total, n	44	38
Study site, n (%)	Radboudumc	15 (39,5)
Gender (%)	male	22 (57,9)
Age, mean (min-max)	61 (43-70)	61 (45-71)
BMI, mean (min-max)	25,8 (17,9-38,2)	26,8 (17,6-38,1)
ECOG, n (%)	0	16 (42,1)
	1	19 (50,0)
	2	3 (7,9)
Disease stage ISS, n (%)	I	12 (31,6)
	II	15 (39,5)
	III	7 (18,4)
	Missing	4 (10,5)
HDM dose mg/kg, mean (min-max)	5,0 (4,1-6,2)	4,9 (3,9-6,1)

FEVER DURING NEUTROPENIA

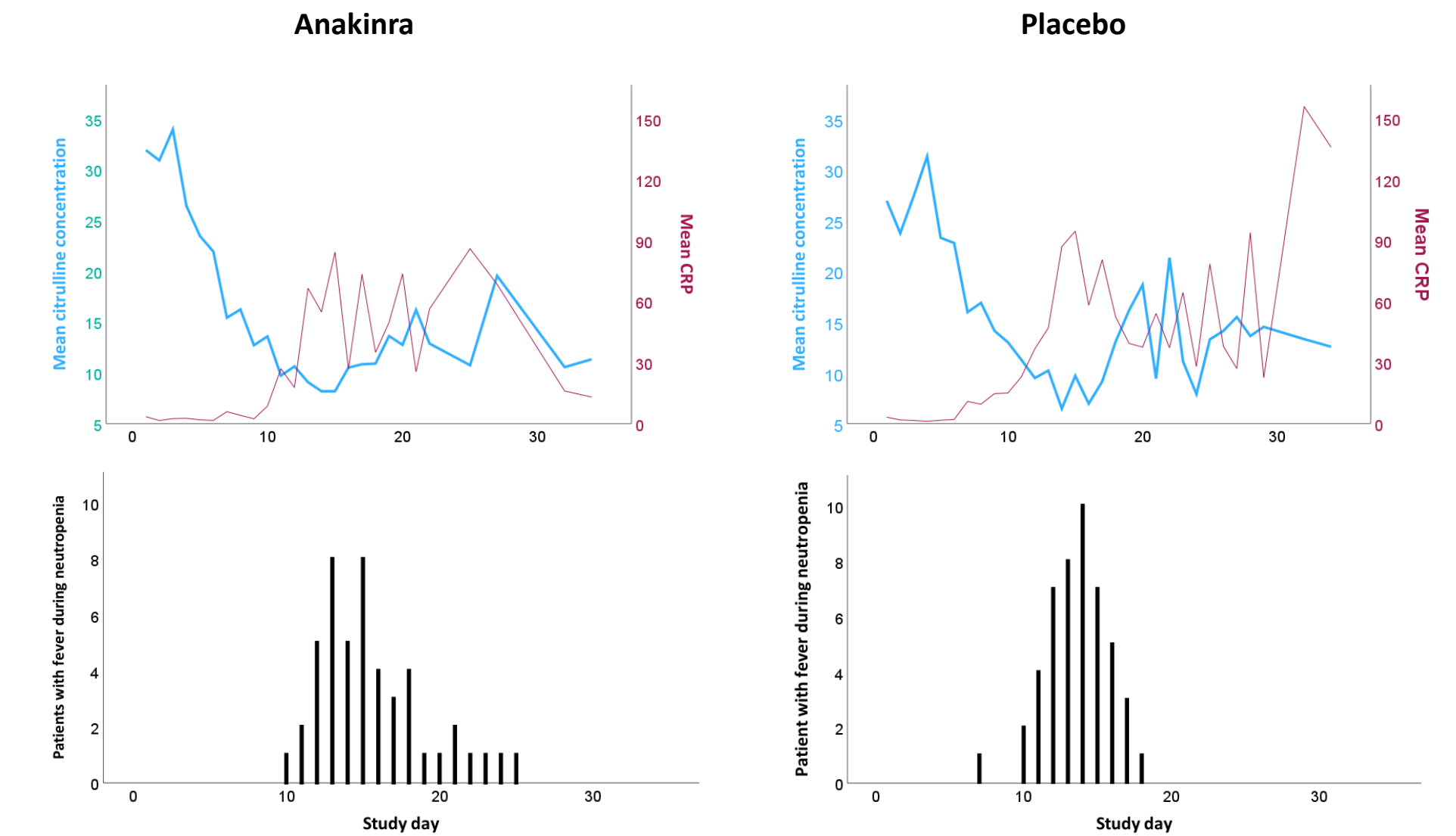


INCIDENCE OF BLOODSTREAM INFECTIONS



MUCOSITIS, SYSTEMIC INFLAMMATION AND FEVER DURING NEUTROPENIA

Figure 2. Mean citrulline concentration, mean CRP and incidence of FN during hospital admission.



Day 1= hospital admission. Day 2= HDM. Day 4= ASCT. Patients were discharged at day 20 on average.

The upper panels depict the relationship between mucositis (citrulline) and systemic inflammation (CRP). When citrulline is at its lowest, CRP is at its highest.

The lower panels show that fever during neutropenia occurs at the same study days that citrulline is <10 umol/L, reflecting severe gut mucositis.

SAFETY

	Anakinra	Placebo
SAE, n	3	4
AE, n	74	57

DISCUSSION

Incidence of FN was lower than anticipated. This could be caused by the standardization of oral cryotherapy reducing oral mucositis. Also, dosage and timing of anakinra needs investigating when it is most beneficial to stop mucositis and forthcoming systemic inflammation.

CONCLUSION

Anakinra did not prevent development of FN nor severe mucositis. Severe intestinal mucositis coincided with clinically defined FN whilst incidence of bloodstream infections was low.

REFERENCES

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