



Maintenance Therapy After Allogeneic Hematopoietic Transplant for Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis

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Background & Objectives

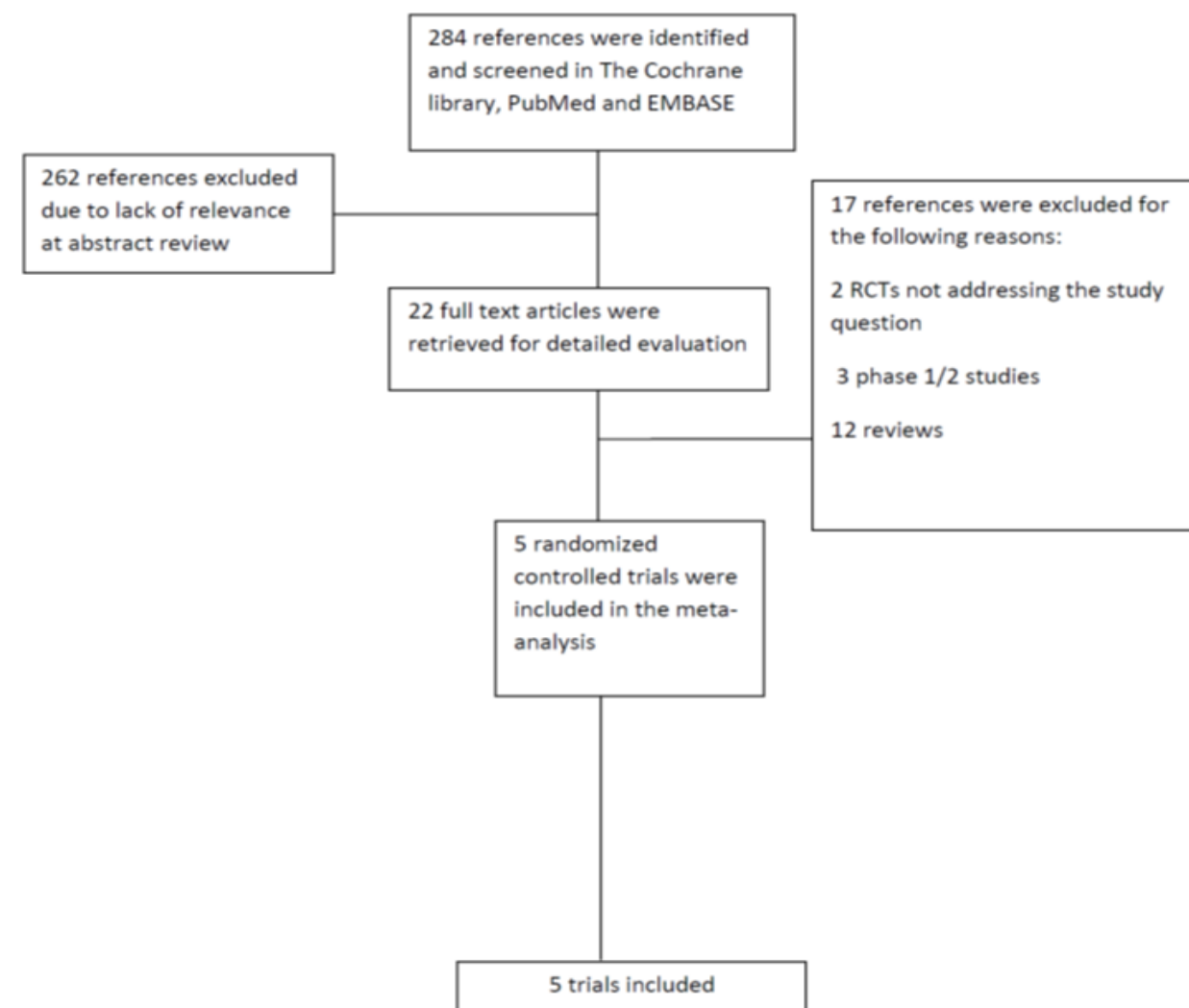
- Allogeneic hematopoietic stem cell transplant (HSCT) is standard frontline therapy for patients with acute myeloid leukemia (AML) when the risk for relapse outweighs projected transplant related morbidity and mortality
- Disease relapse remains the most common reason for transplant failure and patient death
- Different strategies have been explored, aiming to reduce the risk of post-transplant relapse without inflicting excess toxicity
- Recently, several prospective RCTs evaluating the role of maintenance treatment for patients with AML after allogeneic HSCT have been published
- The aim of the present study was to evaluate the efficacy and safety of maintenance therapy for AML patients after allogeneic HSCT.

Materials & Methods

- Systematic review and meta-analysis of randomized controlled trials which compared maintenance therapy with observation or placebo in AML patients after allogeneic HSCT
- We searched PubMed until February 2021; CENTRAL, published in The Cochrane Library, until March 2021, and the following conference proceedings: ASH, ASCO, EHA EBMT and TCT
- We included all randomized controlled trials (RCTs) that compared maintenance therapy with observation or placebo in patients with AML after allogeneic HSCT
- Primary outcome - overall survival (OS)
- Secondary outcomes included relapse free survival (RFS), relapse rate and safety (including adverse events and GVHD)

- Our search yielded 5 trials conducted between the years 2009 and 2018, including 736 patients, all published in peer-reviewed journals (Table 1 & 2)
 - 3 trials included patients with FLT3-ITD mutated AML (the trials with TKI maintenance)
 - 2 trials included patients with high-risk AML.
 - 1 trial also included patients with high risk MDS.

Description of trials



Post-transplant maintenance consisted of:

- TKIs in three trials: sorafenib - two studies^{1,2}; midostaurin³ - one study.
- Hypomethylating agents (HMAs) in two studies: decitabine⁴ and azacitidine⁵ - one study each.

Table 1. Characteristics of included trials

Study	AML type eligibility criteria	Start of maintenance post transplant (days)	Primary endpoint	Length of follow up (months)	Treatment regimen	Number of patients included	Age (Median, range)	Sex (male, percentage)
Burchert 2020	FLT3-ITD mutated AML	60-100	RFS	42	sorafenib	43	54 (24-75)	42%
					placebo	40	54 (19-76)	58%
Maziarz 2020	FLT3-ITD mutated AML	28-60	RFS	24	midostaurin	30	48 (20-61)	53%
					SOC	30	56 (20-68)	60%
Xuan 2020	FLT3-ITD mutated AML	30-60	relapse rate	21	sorafenib	100	35 (26-42)	50%
					SOC	102	35 (26-43)	51%
Gao 2020	High risk AML	60-100	relapse rate	28	decitabine + GCSF	102	30(3-62)	56%
					SOC	102	28(2-52)	60%
Oran 2020	High risk AML/MDS	42-100	RFS	52	azacitidine	93	57 (19-72)	59%
					SOC	94	58 (20-75)	61%

Results

Table 2. Transplant characteristics of included trials

Study	Treatment regimen	Number of patients randomized	Remission at transplant		MRD status at transplant		Conditioning regimen		Donor type		
			CHR	No CHR	MRD+	MRD-	MAC	RIC	MSD	MUD	Haplo
Burchert 2020	sorafenib	43	36	7	27	9	18	25	8	35	0
	placebo	40	31	9	19	12	19	21	12	28	0
Maziarz 2020	midostaurin	30	30	0	NA	NA	28	1	10	20	0
	SOC	30	30	0	NA	NA	27	3	15	15	0
Xuan 2020	sorafenib	100	100	0	NA	NA	100	0	44	8	48
	SOC	102	102	0	NA	NA	102	0	39	6	57
Gao 2020	decitabine + GCSF	102	92	8	24	68	100	0	20	5	75
	SOC	102	97	5	29	68	102	0	16	13	73
Oran 2020	azacitidine	93	55	42	NA	NA	73	14	33	44	4
	SOC	94	45	49	NA	NA	75	18	31	53	5

Primary Outcome:

- Maintenance after allogeneic HSCT was associated with an improved OS, HR=0.61 (95% CI 0.47-0.80) (Fig. 1)
- Subgroup analyses by type of maintenance therapy revealed advantage in OS with either TKI or HMA maintenance [HR=0.50 (95% CI 0.33-0.77) and HR=0.69 (95% CI 0.49-0.98), respectively]

Figure 1

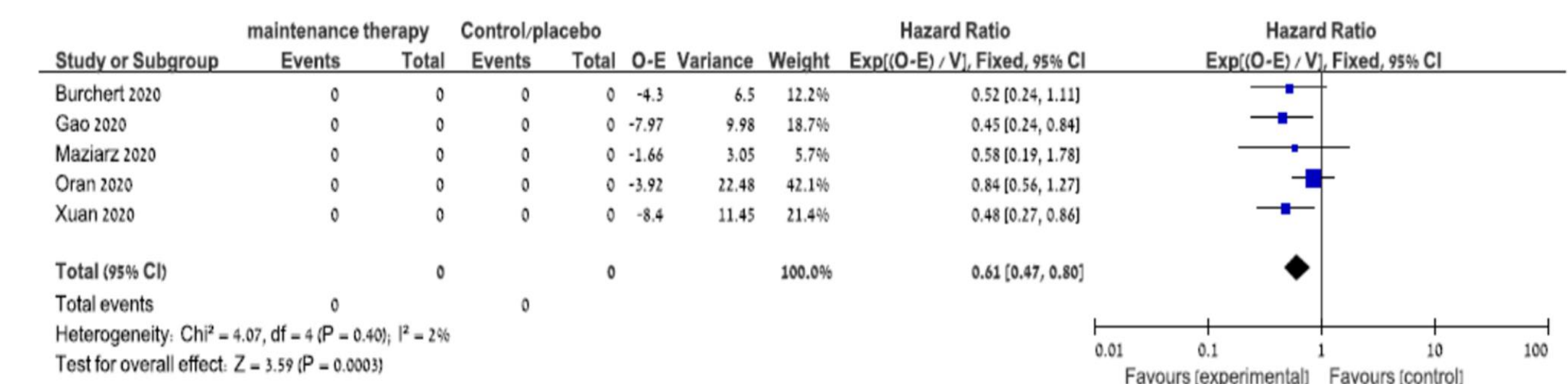
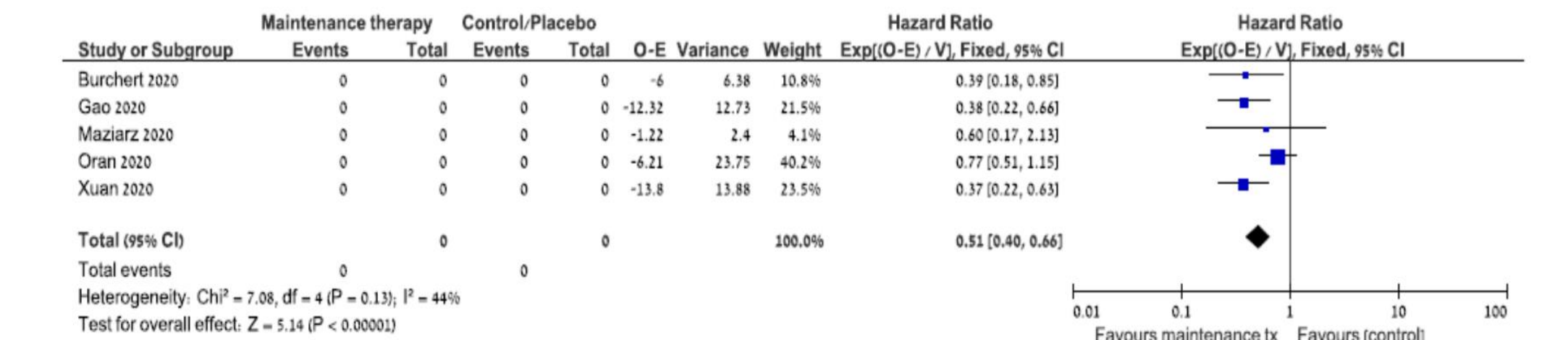


Figure 2



Secondary Outcomes:

- Data from 5 trials was available for RFS analysis and showed improved RFS in the maintenance group compared to the control arm HR=0.51 [95% CI 0.40 - 0.66] (Fig. 2)
- Relapse rate was significantly decreased in the maintenance arm compared to the control arm, RR=0.41 (95% CI 0.20-0.88, 4 trials)
- Regarding safety, there was no difference between the arms concerning adverse events (AE), including grade 3-4 AE, rate of infections and acute and chronic GVHD

Conclusions

- Our meta-analysis shows that post-transplant maintenance therapy in AML patients is effective in decreasing relapse rate and improving RFS and OS, with a satisfactory safety profile
- Future prospective trials could aim to incorporate a broader spectrum of AML patients who could benefit from various post-transplant maintenance regimens

References

- Burchert A, Bug G, Fritz LV, et al. Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3-Internal Tandem Duplication Mutation (SORMAIN). J Clin Oncol. 2020 Sep 10;38(26):2993-3002.
- Xuan L, Wang Y, Huang F, et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. Lancet Oncol. 2020 Sep;21(9):1201-1212.
- Maziarz RT, Levis M, Patnaik MM, et al. Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. Bone Marrow Transplant. 2020 Dec 7.
- Gao L, Zhang Y, Wang S, et al. Effect of rhG-CSF Combined With Decitabine Prophylaxis on Relapse of Patients With High-Risk MRD-Negative AML After HSCT: An Open-Label, Multicenter, Randomized Controlled Trial. J Clin Oncol. 2020 Dec 20;38(36):4249-4259.
- Oran B, de Lima M, Garcia-Manero G, et al. A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients. Blood Adv. 2020 Nov 10;4(21):5580-5588.