■ Sun-372 ■

Addition of metformin to anticancer therapy

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Background/Aims: Preclinical studies have demonstrated that metformin has anticancer properties and act in additive or synergistic way when combined with anticancer agents. We conducted this meta-analysis of randomized, controlled trials to evaluate the effect of metformin added to systemic anticancer therapy in patients with advanced or metastatic cancer **Methods:** A computerized systematic electronic search was performed using the PubMed, Embase, Cochrane Library, and Web of Science databases (up to May 2019). From six randomized, controlled trials, 418 patients were included in the pooled analyses of odds ratios (ORs) with 95% confidence intervals (CIs) for overall response rate (ORR) and hazard ratios (HRs) with 95% CIs for progression-free survival (PFS) and overall survival (OS). **Results:** The combination of metformin with anticancer therapy did not improve tumor response (the pooled OR of ORR = 1.20, 95% CI: 0.72-1.99, *p*=0.48), compared with anticancer therapy alone. In terms of survival, metformin added to anticancer agents failed to prolong PFS (HR = 0.98, 95% CI: 0.71-1.35, *p*=0.90) and OS (HR = 0.95, 95% CI: 0.75-1.21, *p*=0.67). **Conclusions:** This meta-analysis of randomized, controlled trials do not support clinical benefits of metformin added to systemic anticancer therapy in patients with advanced or metastatic cancer.

Figure 1. Flow diagram of search process.

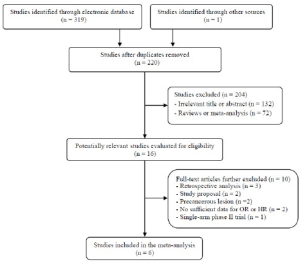

Figure 2. Forest plot for overall response rate.

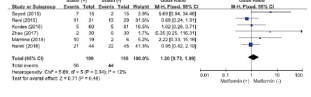

Figure 3. Forest plots for progression-free survival (A) and overall survival (B).

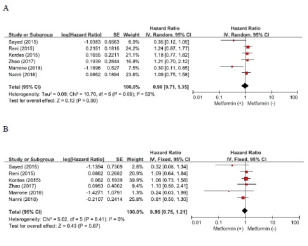

Figure 4. Funnel plots for publication bias: overall response rate (A), progression-free survival (B), and overall survival (C).

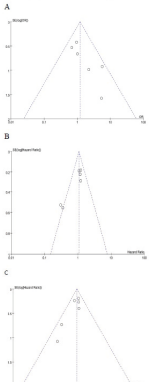

Table 1. Six randomized, controlled trials of metformin addition to systemic anticancer therapy

First author, (year) [ref.]	Cancer type	Phase	Setting	Treatment arm	No. of patients	Primary endpoint	ORR	AEs	mPFS (mo)	HR for PFS (95% CI)	mOS (mo)	HR for OS (95% CI)	Jadad score
Kordes (2015) [20]	PC	II	1st	Gemcitabine/erlotinib + metformin (up to 2 g/d)	60	OS	8.3%	17 (28.3%)[1]	4.1	1.18 (0.77-1.82)	6.8	1.06 (0.73-1.56) $P = 0.78$	5
				Gemcitabine/erlotinib + placebo	61		8.3%	28 (46.7%)[1]	5.4		7.6		
Reni (2016) [21]	PC	II	1st	PEXG + metformin (2 g/d)	31	PFS	35.5%	NA	4.9	1.24 (0.87-1.77) $P = 0.036$	6.83	1.09 (0.64-1.84) $P = 0.13$	3
				PEXG	29		45%	NA	6.1		10.4		
Sayed (2013) [22]	NSCLC	II	1st	Gemcitabine/cisplatin + metformin (500 mg/d)	15	ORR	46.7%	4 (26.7%)[1]	5.54	0.35 (0.12-1.05) $P = 0.062$	12	0.32 (0.08-1.34) $P = 0.119$	3
				Gemcitabine/cisplatin	13		15.3%	10 (66.7%)[1]	3		6.3		
Marrone (2018) [23]	Non-Sq NSCLC	II	1st	Paclitaxel/carboplatin/bevacizumab + metformin (2 g/d)	19	PFS	58%	10 (58%)[1]	9.6	0.30 (0.11-0.85) $P = 0.024$	15.9	0.24 (0.03-1.99) $P = 0.186$	3
				Paclitaxel/carboplatin/bevacizumab	6		33%	2 (33%)[1]	6.7		13.9		
Zhao (2017) [24]	HR(+) BC	II	≥2nd	Aromatase inhibitor + metformin (1 g/d)	30	PFS	6.7%	5 (16.7%)[2]	4.7	1.21 (0.70-2.12) $P = 0.48$	30.9	1.1 (0.50-2.41) $P = 0.81$	5
				Aromatase inhibitor + placebo	30		0%	3 (10%)[2]	6.0		32.4		
Nanni, (2018) [25]	HER2(-) BC	II	1st	Doxorubicin/cyclophosphamide + metformin (2g/d)	57	PFS	48%	31 (54%)[3]	9.4	1.09 (0.75-1.58) $P = 0.653$	34.4	1.09 (0.75-1.58) $P = 0.362$	3
				Doxorubicin/cyclophosphamide	65		49%	47 (72%)[3]	9.9		26.8		

PC, pancreatic cancer; NSCLC, non-small-cell lung cancer; non-Sq, non-squamous; HR(+), hormone positive; Her2(-), HER2 negative; PEXG, cisplatin, epirubicin, capecitabine, and gemcitabine; AEs, adverse events; ORR, overall response rate; mOS, median overall survival; mPFS, median progression-free survival; mo, months; HR, hazard ratio; CI, confidence interval; NA, not available.

[1]Vomiting, [2]Nausea, [3]Grade 3-4 neutropenia, [4]Arthralgia