Ellagic Acid and Annona Muricata in association with a short course of intravescical prophylaxis in non muscle invasive bladder cancer. A prospective non randomized observational study

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Aims of Study:

Ellagic acid (EA) is a polyphenolic naturally present in pomegranates, berries, grapes, green tea and nuts. The antitumor effect of EA has been reported in vitro against different human bladder cancer cell lines. it could down-regulate the expression of programmed cell death ligand 1 (PD-L1). Annona muricata (AM) is a small tropical evergreen fruit tree whose therapeutic benefits against various human tumors have been reported in vitro culture and in preclinical animal models. We present a preliminary prospective study on the activity of a combination of EA and AM in short term prevention of recurrence after an induction cycle of intravesical chemotherapy or BCG.

Methods:

Patient affected by non-muscle invasive bladder cancer (NMIBC) after transurethral resection and intravesical prophylaxis with an induction 6-week cycle of chemotherapy or BCG were entered in a prospective observational non randomized trial. The patients were subdivided into two groups in relation to the oral assumption of 100 mg of EA plus 100 mg of AM daily for 6 months. All patients were submitted to 3-month cytology and cystoscopy.

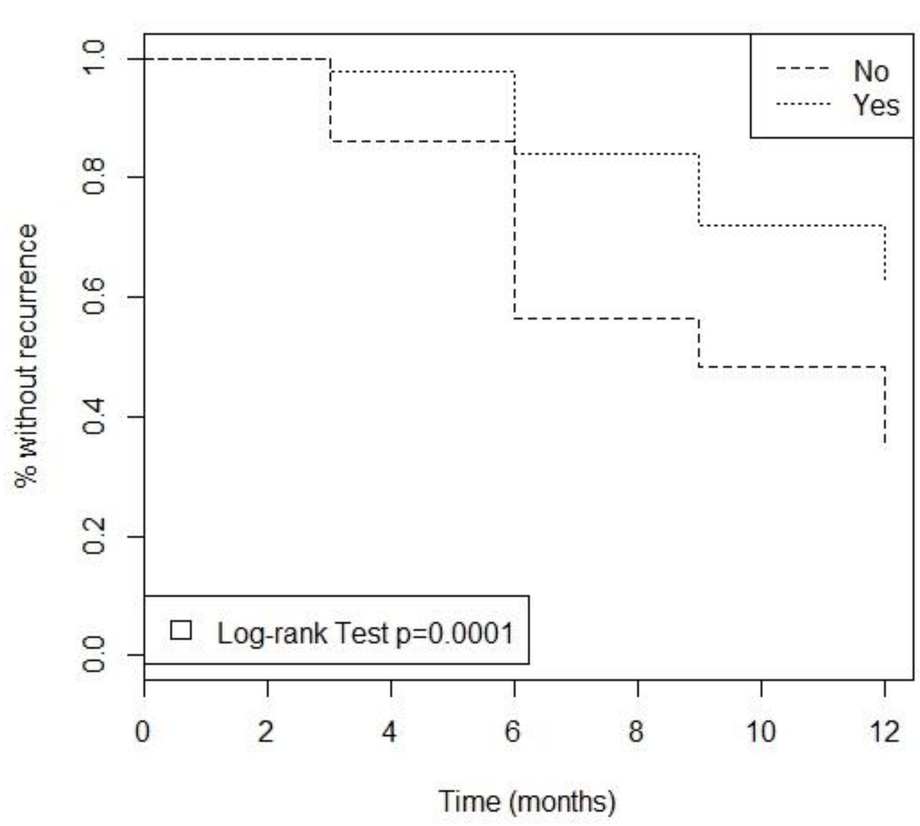

Figure 1
RFS according to AE+AM treatment

	Ellagic Acid				
	Yes	**No**	**Total**	**P-value**	Pts n°
Patients, n (%)	90 (56%)	72 (44%)	162		
Gender				0,6777	n=159
Female	18 (20%)	12 (17,4%)	30 (18,9%)		
Male	72 (80%)	57 (82,6%)	129 (81,1%)		
T-stage				0,885	n=157
Ta	50 (56,8%)	40 (58%)	90 (57,3%)		
T1	38 (43,2%)	29 (42%)	67 (42,7%)		
Grade				0,151	n=157
LG	18 (20,5%)	21 (30,4%)	39 (24,8%)		
HG	70 (79,5%)	48 (69,6%)	118 (75,2%)		
Previous history				0,899	n=161
Primitive	46 (51,1%)	37 (52,1%)	83 (51,6%)		
Recurrent	44 (48,9%)	34 (47,9%)	78 (48,4%)		
Focality				0,464	n=160
Single	54 (60,7%)	39 (54,9%)	93 (58,1%)		
Multiple	35 (39,3%)	32 (45,1%)	67 (41,9%)		
Drug				0,134	n=160
BCG	52 (59,1%)	34 (47,2%)	86 (53,8%)		
Chemotherapy	36 (40,9%)	38 (52,8%)	74 (46,2%)		
Early instillation				0,507	n=159
Yes	2 (2,3%)	3 (4,2%)	5 (3,1%)		
No	85 (97,7%)	69 (95,8%)	154 (96,9%)		

Table 1. Association of clinic and pathologic features of 162 patients divided in two groups according to the assumption of EA+AM

Results:

Out of 180 entered patients, 162 (90%) are evaluable, 90 and 72 receiving or not EA+AM, respectively. No statistically significant difference emerged between the 2 groups in patients' characteristics. BCG was given in 86 (53.8%) and chemotherapy in 74 (46.2%) patients. Early instillation preceding the 6-week cycle was administered in 5 patients (3.1%). Only 2 (2.2%) patients interrupted prematurely the assumption of EA+AM and 8 (4.9%) were lost at follow-up before the first cystoscopy. At 3, 6 and 12 months, 12 (7.9%), 43 (28.3%) and 73 (48.0%) patients recurred. The recurrence free rate at 3, 6 and 12 months in patients assuming or not EA was 96.5% versus 84.6% (p=0.003), 85.4% versus 64.8% (p=0.005) and 74.2% versus 60.6% (p=0.246), respectively. The recurrence free survival at 12 months in patients assuming or not EA was 63.0% versus 34.5%. (p<0.0001) (Fig.1).

Conclusion:

Main limits of our study are the non randomized design, the limited number of patients and the short follow-up. The results obtained should be considered as preliminary and obtained by a pilot investigation. In our preliminary observational study EA oral assumption for 6 months seems to enhance the prophylactic efficacy of traditional intravesical treatment.

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