Randomized trial with BIALOE® to prevent esophagitis in lung cancer patients treated with concurrent radical chemoradiotherapy.

F. Casas[1], J. Jové[2], N. Toscas[3], D. Muñoz-Guglielmetti[1], TD. Barreto[1], F. Pagan[1], M. Mollà[1].

Hospital Clínic de Barcelona[1], Spain. Hospital Germans Trias i Pujol[2], Badalona, Spain. Clinica Teknon, Barcelona, Spain[3].

DISCLOSURES

Commercial Interest	Relationship(s)
F. Casas	Advisory Board and Consultant of Atlantia Company
J. Jové	Consultant of Atlantia Company
N. Toscas	Consultant of Atlantia Company

BACKGROUND

Acute radiation esophagitis (ARE) is a frequent complication of chemoradiotherapy (CRT). In 2014, a retrospective study performed at Hospital Clínic de Barcelona with lung cancer (LC) patients treated with CRT. By incorporating drinkable BIALOE® (20 mg) during treatment, delay in the onset of ARE symptoms and in the need for analgesia compared to historical controls.

BIALOE® is a pure juice of aloe vera, organically grown in the volcanic soil of the Canary Islands, with favorable climatic conditions. The extraction and processing techniques preserve the natural properties of this plant.

We performed a multicenter randomized, double-blind trial including advanced, inoperable LC patients treated with concurrent platinum-based CRT.

MATERIAL AND METHODS

Patients with NSCLC received concurrent CRT with a doublet based cisplatin or carboplatin and standard fractionation RT till 60 Gy. On the other hand, SCLC received concurrent CRT with a doublet based cisplatin or carboplatin plus etoposide and hyperfractionated RT till 45 Gy.

BIALOE® was administered orally in doses of 20 ml, every day before each RT session until 10 days after completion of CRT. The placebo group received a drink from the same bottle as the original BIALOE®.

Sample size calculated according to figure:

$$n = \frac{\left[Z_\alpha * \sqrt{2p(1-p)} + Z_\beta * \sqrt{p_1(1-p_1) + p_2(1-p_2)}\right]^2}{(p_1 - p_2)}$$

Zα= Z value corresponding to the confidence level
Zβ= Z value corresponding to the risk
p1= Proportion of placebo group
p2= Proportion of BIALOE group
p= Mean of the 2 proportions (p1 and p2)

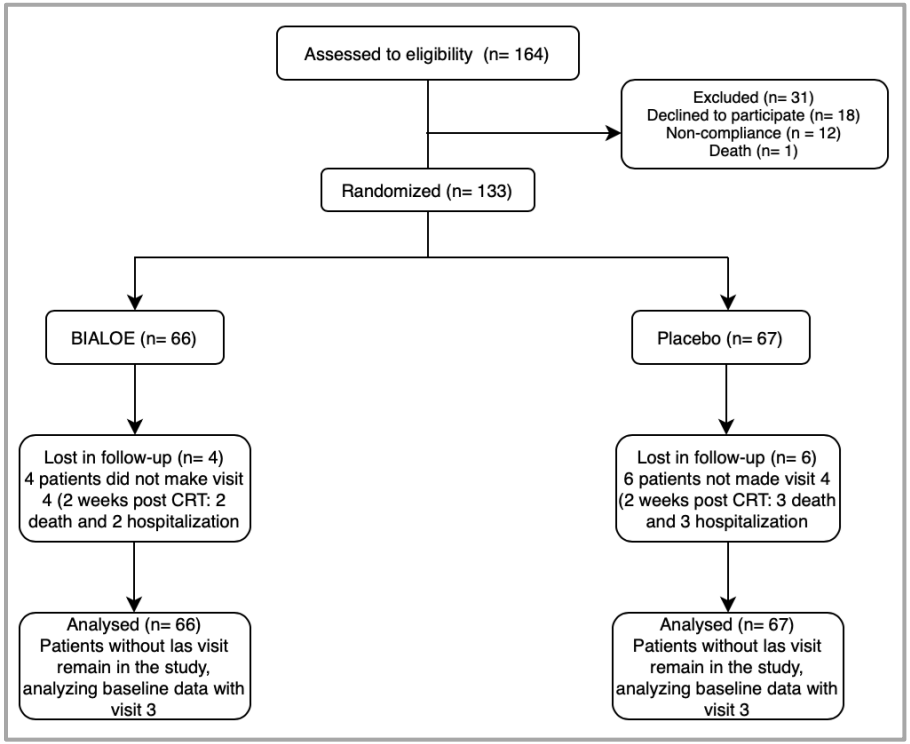
MATERIAL AND METHODS

Clinical evaluation was performed on a baseline basis in the treatment planning, during the RT at 20, 40 and 60 Gy, and 15 days after finishing CRT.

The dosimetric parameters evaluated include the length and volume of esophagus (E) treated, the percentage of the E volume treated at V10 to V60 Gy. Percentage of complete circumference of E length (%CCEL) and percentage of partial circumference of E length (%PCEL).

Primary endpoint: Incidence of ARE ≥G2.

Secondary endpoints: Pain evaluation, need for analgesia, quality of life (QoL C30) and oral intake.



RESULTS

7 hospital participated with 164 patients assessed for eligibility between october 2016 to september 2019. The study closed prematurely because only 3 hospitals were able to actively recruit patients.

Finally, 133 patients were randomized, 66 to BIALOE® and 67 to placebo.

	BIALOE® (n= 66)	Placebo (n= 67)
Age		
< 60	22 (33.3%)	17 (25.4%)
60-70	24 (36.4%)	27 (20.3%)
> 70	20 (30.3%)	21 (31.3%)
Male	51 (77.3%)	49 (73.1%)
Smoke	10 (15.2%)	8 (11.9%)
Comorbidities	26 (39.4%)	31 (46.3%)
Antacid use	29 (43.9%)	27 (40.3%)

Patients characteristics

	BIALOE® (n= 66)	Placebo (n= 67)
T1 N2	5 (7.6%)	5 (7.5%)
T1 N3	2 (3.0%)	0
T2 N0	1 (1.5%)	1 (1.5%)
T2 N1	1 (1.5%)	2 (3.0%)
T2 N2	9 (13.6%)	18 (26.9%)
T2 N3	2 (3.0%)	2 (3.0%)
T3 N0	1 (1.5%)	1 (1.5%)
T3 N1	1 (1.5%)	0
T3 N2	12 (18.2%)	11 (16.4%)
T3 N3	6 (9.1%)	5 (7.5%)
T3 Nx	0	1 (1.5%)
T4 N0	6 (9.1%)	5 (7.5%)
T4 N1	2 (3.0%)	2 (3.0%)
T4 N2	11 (16.7%)	6 (9.0%)
T4 N3	5 (7.6%)	4 (6.0%)
Tx N2	0	3 (4.5%)
Tx N3	2 (3.0%)	1 (1.5%)

Tumor characteristics

RESULTS

No differences in the incidence of ARE ≥G2.

Patients with ARE presented significant difference between %CCEL 20 Gy and 30 Gy with mean differences of 14.8 (p= 0.026) and 13.9 (p= 0.021), respectively, in favor of BIALOE®.

In the hyperfractionated RT group the mean dose to the E was 8.8 (p= 0.046) with %CCEL 40 Gy 20.6 (p= 0.039) in favour of BIALOE®.

In the patients pain valoration, BIALOE® patients presented fewer differences between baseline and at end of CRT, and two weeks after finishing CRT.

		≠μ (C.I 95%)	*p* value
Esophagitis	**%CCEL 20 Gy**	14.8 (1.9 - 27.6)	0.026
	%CCEL 30 Gy	13.9 (2.2 - 25.5)	0.021
Esophagitis and hyperfractionated RT	**Mean dose to E**	8.8 (0.2 - 17.4)	0.046
	%CCEL 40 Gy	20.6 (1.1 - 40.1)	0.039

Differences in means between BIALOE® and Placebo in patients with esophagitis. E= Esophagus; %CCEL= Percentage of complete circumference of E length.

CONCLUSIONS

This is the only phase III clinical trial with aloe vera that analyses prospectively the role in ARE in LC .

Since the acute toxicity of RT is higher and earlier in hyperfractionated schemes, it seems that BIALOE® has a greater protective action in this group of patients

The main limitation of our study is the size of the sample. According to the initial calculation, 220 patients were required, so the necessary statistical power (90%) was not reached.

Another point to consider is the absence of information on the level of neutropenia, which is a relevant factor in the pathogenesis of acute esophagitis