Overview

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Title: A Phase IIb Trial Assessing the Addition of Disulfiram to Chemotherapy for the Treatment of Metastatic Non-Small Cell Lung Cancer

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Amichai Baron: Ora Bio Ltd. (RF, E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

Disulfiram, an alcohol aversion agent, has been in use for >50 years. Numerous authors have reported an anticancer effect of this drug in vitro and in mouse models. More recently, several reports have claimed that disulfiram also possesses anti-stem cell activity. We set out to obtain initial data regarding the safety of combining this drug with chemotherapy and the possible effectiveness of disulfiram in a combination regimen in non-small cell lung cancer (NSCLC).

Methods

This phase II, multicenter, randomized, double-blinded study assessed the safety and efficacy of adding of disulfiram to cisplatin and vinorelbine for six cycles. Newly diagnosed NSCLC patients were recruited. Patients with either stage IV or what was considered at the time "wet IIIb" (since 2009, these patients have been considered stage IV) were recruited. The patients were treated with only chemotherapy, and none were treated with either surgery or chemoradiation. Disulfiram was administered at a dose of 40 mg three times daily.

Results

Forty patients were treated for more than two cycles, half with and half without disulfiram, which was well tolerated. An increase in survival was noted for the experimental group (10 vs. 7.1 months). Interestingly, there were only two long-term survivors, both in the disulfiram group.

Conclusion

The addition of disulfiram to a combination regimen of cisplatin and vinorelbine was well tolerated and appeared to prolong survival in patients with newly diagnosed non-small cell lung cancer. The results from this small study seem encouraging

enough for assessment in larger trials. Disulfiram is an inexpensive and safe drug; if its addition to chemotherapy could be shown to prolong survival, an effective regimen could be established and used widely, even in resource-poor countries.

Discussion

Given preclinical data suggesting antitumor activity and its established safety, there is interest in the use of disulfiram as an anticancer drug [1, 2]. To our knowledge, this randomized trial is the first using disulfiram as an additional anticancer treatment in lung cancer. Although its precise mechanisms of action have yet to be established, preclinical studies have suggested that disulfiram possesses antiangiogenic activity and can inhibit the activity of ATP-binding cassette transporters [3]. Additional activity of disulfiram has been suggested recently: inhibition of cancer stem cells. The latter is thought to be a consequence of disulfiram's inhibitory effect on aldehyde dehydrogenase, an enzyme that is highly expressed in what many believe are cancer stem cells [4]. Kim et al. recently demonstrated that the use of disulfiram can induce apoptosis in pancreatic cancer stem cells expressing high levels of aldehyde dehydrogenase [5]. This finding suggests that disulfiram's anti-cancer stem cell activity may be of great importance, especially in tumors that have an initial response to the therapy.

In this paper, we described a phase II trial of a regimen using cisplatin plus vinorelbine with or without disulfiram in lung cancer. Disulfiram was continued after cessation of chemotherapy after six cycles. Analysis was performed on the 40 patients who continued treatment beyond the first two cycles. The higher response rate (46% vs. 37%) in the disulfiram group was not statistically different. Quality of life was similar between the groups; however, it is noteworthy that both progression-free and overall survival curves separate, and because of the long-term response of a few patients in the active group, there is a statistically significant progression-free and overall survival advantage for the active group (Fig. 1).

The unusual result is the long-term survival of two patients in the active group, an event that is extremely rare in patients with stage IV lung cancer treated by chemotherapy alone. It is important to note that the difference in survival continued after cessation of chemotherapy and maintenance with disulfiram alone.

The drug is inexpensive, and its tolerability and safety have been demonstrated over years of clinical experience with a large number of patients. Our results support a larger phase III trial combining this drug with chemotherapy.

Trial Information

Disease	Lung cancer – NSCLC
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Randomized
PFS	P: 0.043, HR:
Primary Endpoint	Progression-free survival
Primary Endpoint	Overall survival
Secondary Endpoint	Tolerability
Additional Details of Endpoints or Study Design	All patients of this double-blind trial had agreed to abstain from alcohol drinking. Tolerability was assessed by quality of life questionnaires and was similar in both groups, which abstained from alcohol. Fifty-three patients were initially recruited, but results are presented only for the 40 patients who continued following the first two cycles and were divided into two similar sized groups. Disease responded in 10 patients in the experimental group and in 7 patients in the control group.
Investigator's Analysis	Active and should be pursued further

Drug Information

Experimental Arm

Drug 1	
Generic/Working name	Disulfiram
Trade name	Antabuse

Company name	Ora Bio (just the preparation of the capsules)
Drug type	Small molecule
Drug class	Other
Dose	40 × 3 day milligrams per flat dose
Route	Oral (po)
Schedule of Administration	Three times daily versus placebo. Drug was compared with placebo and used even following cessation of therapy. The drug was added to standard dose of cisplatin (75 mg/m^2) every 3 weeks and vinorelbine 25 mg/m^2 days 1 and 8.
Drug 2 **Generic/Working name**	Cisplatin
Trade name	Platinol
Drug type	Other
Drug class	Alkylating agent
Dose	75 mg per m^2
Route	IV
Schedule of Administration	Every 3 weeks
Drug 3 **Generic/Working name**	Vinorelbine
Trade name	Navelbine
Drug class	Other
Dose	25 mg per m^2
Route	IV
Schedule of Administration	Days 1 and 8 every 3 weeks

Patient Characteristics

Number of patients, male	40		
Number of patients, female	13		
Stage	4		
Age	Median (range): Age (Median) Control 62.3; Disulfiram 60.4		
Number of prior systemic therapies	Median (range): 0		
Performance Status:	ECOG 0 — 1 — 2 — 3 — unknown —		
Other: Number of Subjects by Visit		**Control**	**Disulfiram**
	Screening	27	26
	Cycle 1 day 8	25	24
	Cycle 2 day 1	23	23
	Cycle 3 day 1	19	21
	Cycle 4 day 1	19	19
	Cycle 5 day 1	17	16
	Cycle 6 day 1	15	15
Cancer Types or Histologic Subtypes	Non-small cell lung cancer ECOG 0–1		

Primary Assessment Method

Control Arm: Non-small cell lung cancer

Number of patients screened	27
Number of patients enrolled	19
Number of patients evaluable for toxicity	19
Number of patients evaluated for efficacy	19
Evaluation method	Other
Response assessment CR	0
Response assessment PR	36.8
Response assessment SD	47.4
Response assessment PD	15.4
(Median) duration assessments PFS	4.9 months
(Median) duration assessments TTP	4.9 months
(Median) duration assessments OS	7.1 months

Experimental Arm: Non-small cell lung cancer

Number of patients screened	26
Number of patients enrolled	21
Number of patients evaluable for toxicity	21
Number of patients evaluated for efficacy	21
Evaluation method	Other
Response assessment CR	4.8
Response assessment PR	42.9
Response assessment SD	52.4
Response assessment PD	0
(Median) duration assessments PFS	5.9 months
(Median) duration assessments TTP	6.7 months
(Median) duration assessments OS	10.0 months

Adverse Events Control Arm

Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All Grades
Cardiac ischemia/infarction	96.15%	0.0%	0.0%	0.0%	3.85%	0.0%	3.0%
Neutrophils/granulocytes (ANC/AGC)	96.15%	3.85%	0.0%	0.0%	0.0%	0.0%	3.0%
Nausea	69.23%	7.69%	19.23%	3.85%	0.0%	0.0%	30.0%
Fatigue (asthenia, lethargy, malaise)	92.31%	3.85%	3.85%	0.0%	0.0%	0.0%	7.0%

Adverse Events Legend
*No Change from Baseline/No Adverse Event
The study used relatively high-dose cisplatin and vinorelbine. It was performed before aprepitant and/or palonosetron were available; hence, it is not surprising that high percentages of vomiting and nausea were noted.
It seems that side effects were relatively very similar in the control and the experimental groups.
There were 22 of 27 adverse events in the active and 21 of 26 in the control groups.
Patients generally refrained from drinking alcohol during this trial, and there were no serious events noted as "Antabuse syndrome." There were two cases of myocardial infarction: one in the control group and one in the experimental group, both in the first cycle. In fact, all the serious adverse events happened in the first two cycles and were similar between control and experimental groups. We have not included those patients in the efficacy analysis.
It is also noteworthy that quality of life questionnaires revealed a slight increase in QOL in the experimental versus control group.

Serious Adverse Events Control Arm

Name	Grade	Attribution
Myocardial infarction	4	Possible

Serious Adverse Events Legend
Altogether in the first cycle there were 9 serious adverse events noted in the experimental group with 6 of those removed from the study and 8 adverse events in the control group with 7 of those removed from further study.
Two patients in the experimental group and one in the control group died in the first cycle.

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not collected
Investigator's Assessment	Active and should be pursued further

Discussion

In this phase IIb trial, we used a combination of disulfiram and a well-described cisplatin-based doublet of cisplatin and vinorelbine. This treatment was one of the most commonly used at the time, and we added disulfiram mainly because of our knowledge of its antiangiogenic activity. It is noteworthy that even now, with the addition of pemetrexed or bevacizumab to our anticancer arsenal, the improvement in overall patient survival was only incremental at ~10 weeks. Both of these drugs are still very expensive, thus the results from the current trial may still be relevant, even with the addition of new anti-lung cancer drugs.

Both overall and progression-free survival curves in the trial separated after a few months. It seemed that many of the patients progressed rapidly without any significant response to the chemotherapy or its combination with disulfiram. However, the separation of the curves after a few months and the relatively long survival of a few patients in the experimental arm suggest that a subpopulation of cancer patients might have greater sensitivity to the addition of disulfiram. The very long survival of two of these patients might be just a chance occurrence but is still intriguing.

An interesting hypothesis is that the addition of disulfiram helps in depletion of the so-called cancer stem cell population. Disulfiram is an inexpensive and well-tolerated compound that has been used widely for alcohol aversion therapy. A larger relatively simple phase III trial adding disulfiram to current platinum-based therapies in lung cancer may have merit. Such a trial, hopefully, could be carried out at a relatively low cost without any special infrastructure in countries that currently do not use bevacizumab or pemetrexed as standard therapy.

Another very interesting avenue of research that could be pursued in a much smaller but more technically demanding trial is a study of the in vivo effects of disulfiram on the so-called cancer stem cell population. This could be performed in the neoadjuvant setting by assessing the percentages of cancer stem cells with and without disulfiram before and after therapy. Such a trial could provide important insights into the mechanism of disulfiram activity.

Acknowledgment

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References

1. Barth KS, Malcolm RJ. Disulfiram: An old therapeutic with new applications. CNS Neurol Disord Drug Targets 2010;9:5–12.
2. Cvek B. Nonprofit drugs as the salvation of the world's healthcare systems: The case of Antabuse (disulfiram). Drug Discov Today 2012;17: 409–412.
3. Marikovsky M, Nevo N, Vadai E et al. Cu/Zn superoxide dismutase plays a role in angiogenesis. Int J Cancer 2002;97:34–41.
4. O'Flaherty JD, Barr M, Fennell D et al. The cancer stem-cell hypothesis: Its emerging role in lung cancer biology and its relevance for future therapy. J Thorac Oncol 2012;7:1880–1890.
5. Kim SK, Kim H, Lee DH et al. Reversing the intractable nature of pancreatic cancer by selectively targeting ALDH-high, therapy-resistant cancer cells. PLoS One 2013;8:e78130.

Figures and Tables

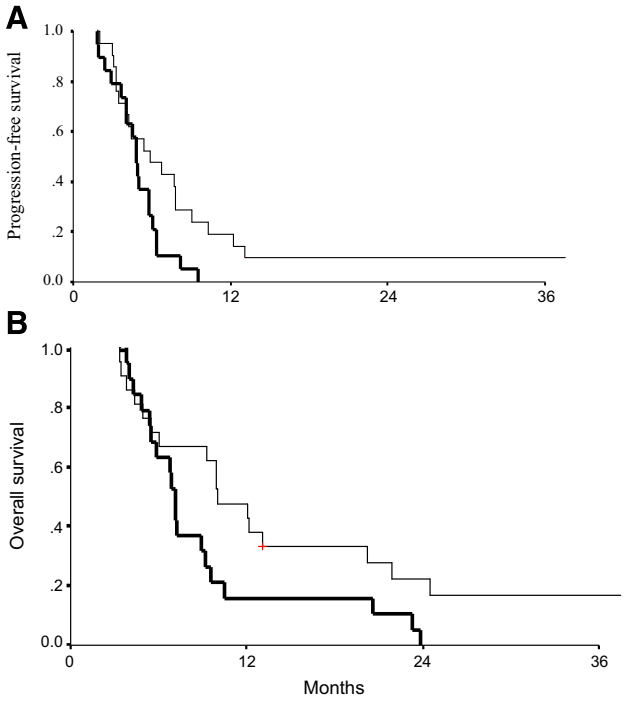

Figure 1. Progression-free survival (5.9 vs. 4.9 months; $p = .043$) **(A)** and overall survival (10.0 vs. 7.1 months; $p = .041$) **(B)** of patients in this phase II trial. Controls were treated with six cycles of cisplatin and vinorelbine (plus placebo tablets), and experimental groups were treated with the same treatment plus the addition of disulfiram, which was continued for stable or responding patients. Improvement in both progression-free and overall survival seems to have happened only after a few months.

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