Supplementary Online Content

Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: The TIME2 randomized controlled trial. *JAMA*. 2012. doi:10.1001/jama.2012.5535.

eSupplement. Methods, Trial Outcomes, Statistical Methods, Results, Baseline Characteristics, and References

This supplementary material has been provided by the authors to give readers additional information about their work.

Methods

Other assessments were the Chronic Respiratory Disease Questionnaire (CRDQ),) and the EuroQol-5 Dimension (EQ-5D) Questionnaire) and spirometry at all follow up visits. Temperature was recorded twice daily for the first 7 days.

Other trial outcomes

a) Proportion of patients achieving clinically significant difference in mean VAS chest pain over first 42 days (13mm[1])
b) Proportion of patients with a fever (defined as a temperature > 37.5 degrees Celsius) during the first 7 days after randomisation.
c) FEV1 (ml) at 6, 10, 14, 18, 22 and 26 weeks and 9 and 12 months.
d) FVC (ml) at 6, 10, 14, 18, 22 and 26 weeks and 9 and 12 months.
e) Proportion using oxygen at 6, 10, 14, 18, 22 and 26 weeks and 9 and 12 months.
f) Proportion using opiates at 6, 10, 14, 18, 22 and 26 weeks and 9 and 12 months.
g) Proportion using opiates or oxygen at 6, 10, 14, 18, 22 and 26 weeks and 9 and 12 months.
h) Proportion treated with chemotherapy up to one year
i) Total CRDQ score
j) Dyspnoea domain of CRDQ score
k) Mastery domain of CRDQ score

The results of the EQ-5D will be reported in a further paper reporting cost efficacy.

Statistical Methods

Data were analysed on an intention-to-treat basis and all randomized patients in whom an outcome was available were included in the analysis. All analyses were pre-determined prior to any data analysis, unless specifically stated. Analyses were adjusted for the minimisation variables (performance status and mesothelioma). Stata version 12.1 was used.

The difference between treatment arms in mean daily dyspnea and chest pain VAS score over 42 days was calculated using a mixed-effects linear regression model. This approach was used to account for days with missing VAS scores (the analysis did not differentiate between scores missing due to patient death and those missing because the patient did not complete their VAS score on that day). Study day was modelled as a continuous variable using fractional polynomials and was included in the model as a random effect. The model adjusted for the baseline VAS score and mean imputation was used for patients on whom a baseline score was unavailable.

A number of sensitivity analyses were performed to ensure robustness of the primary analysis. A complete case analysis was performed, where the mean VAS score over 42 days was calculated for each patient (days with missing VAS scores were ignored). Results were analysed using a linear regression model.

Next, multiple imputation was used to account for days with missing VAS scores. Follow-up was divided into six one-week periods, and mean dyspnea intensity was calculated for each period. If more than 3/7 VAS scores were missing in a period, the mean dyspnea intensity was set to missing. Multiple imputation using chained equations was then used to impute periods with missing VAS scores. 50 imputations were used, and results were combined using Rubin's Rules. The imputation model included the mean VAS score in each follow-up period, and imputations were done separately by treatment groups.

A number of sensitivity analyses assessed robustness to departures from the missing-at-random assumption. Multiple imputation was performed as above, however missing data was assumed to be missing-not-at-random. Missing-not-at-random data was imputed by first imputing missing-at-random data, and then adding a set amount y to each imputed outcome. The amount y that is added to the imputed values can be thought of as the mean difference in VAS score between patients with observed data and those whose data is missing (conditional on any other covariates in the imputation model). We y values of -10, -5, 5, 10, and 20 (positive y values indicate patients with missing VAS scores had worse dyspnea than those with observed scores, and vice versa).

All-cause mortality was to be analysed using a Cox regression model however preliminary investigations during data analysis showed that the proportional hazards assumption was violated. Analysis was therefore based on restricted mean survival time which does not make any assumptions regarding proportional hazards[2]. A Kaplan-Meier graph showed crossing hazards, so it was hypothesized that one treatment may provide an early advantage whereas the other treatment may provide a late advantage. We therefore estimated treatment effects at 6 weeks and at 3, 6, 9, and 12 months.

Results

Primary outcome – sensitivity analyses

A complete case analysis showed no significant difference in dyspnea intensity between treatment groups (difference (IPC vs talc) 0.1, 95% CI -7.0 to 7.2, p=0.97).

Using multiple imputation and assuming missing data were missing-at-random showed similar results (difference (IPC vs talc) -0.3, 95% CI -9.3 to 8.7, p=0.94).

Results were similar under missing-at-random scenarios;

y=-10; (difference (IPC vs talc) 0.9, 95% CI -8.1 to 9.9, p=0.85)
y=-5; (difference (IPC vs talc) 0.3, 95% CI -8.7 to 9.2, p=0.95)
y=5; (difference (IPC vs talc) -1.0, 95% CI -10.1 to 8.1, p=0.83)
y=10; (difference (IPC vs talc) -1.6, 95% CI -10.8 to 7.6, p=0.73)
y=20; (difference (IPC vs talc) -2.8, 95% CI -12.4 to 6.8, p=0.56)

Chest pain VAS scores calculated at 10, 14, 18, 22 and 26 weeks, and 9 and 12 months

No significant difference in chest pain was observed between groups for the duration of the trial, with difference in mean VAS (IPC vs. talc) at day 42 = 1.1mm, 95% CI -5.3 to 7.6, p=0.73; and 0.7mm, 95% CI -5.7 to 7.0, p=0.84, respectively. At 6 months = -0.6mm, 95% CI -15.2 to 14.1, p=0.94 and -0.3mm, 95% CI, -15.5 to 15.0, p=0.97, respectively.

Proportion of patients with a fever (>37.5°C) during the first 7 days after randomization

Over the first seven days the median number of recorded temperatures was 11/14 (IQR 7-13) in the IPC group and 8/14 (IQR 6-14) in talc group. There was a non-significant trend towards an increased temperature during the first 7 days for patients in the talc group (talc 17% vs. IPC 2.4%; OR = 0.54, 95% CI 0.15 to 1.90, p=0.33).

Proportion of patients achieving clinically significant difference in mean VAS chest pain over 42 days

Twelve (26%) patients in the talc group and 17 (35%) in the IPC group had a clinically significant improvement in chest pain intensity (OR IPC v. talc 0.75, p=0.77).

eTable. Further baseline characteristics

	IPC	Talc
Cytology positive v. negative	27:23	27:25
Performance status (ratio 0-1:2-3) (% 0-1)	30:22 (58)	30:24 (56)
No. receiving chemotherapy at enrolment (%)	8 (15)	5 (9)
No. using opiates at enrolment (%)	19 (37)	10 (19)
No. using oxygen at enrolment (%)	9 (17)	6 (11)
FEV1 (SD), ml	1100 (400)	1200 (450)
FVC (SD), ml	1400 (540)	1500 (570)
EORTC: Dyspnoea	80 (24)	82 (23)
CRDQ total	13 (3.4)	13 (3.7)
CRDQ mastery	4.0 (1.2)	3.7 (1.2)
CRDQ dyspnoea	2.6 (0.8)	3.0 (1.1)

References

1.   Li SF, Greenwald PW, Gennis P, Bijur PE, Gallagher EJ. Effect of age on acute pain perception of a standardized stimulus in the emergency department. *Ann Emerg Med.* Dec 2001;38(6):644-647.
2.   Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med.* Aug 30;30(19):2409-2421.