Dominic LaRoche

Elinora Price

CPH 576C

Project 3

11/12/14

Longitudinal Analysis of Quality of Life in Advanced Lung Cancer Patients

In the study of cancer and its treatment, quality of life of patients undergoing treatment has become an important area of interest.  However, assessment of quality of life over a treatment period is intrinsically complicated by loss of observations, especially due to severe illness or death.   In this study we evaluate and compare the quality of life of over time of advanced lung cancer patients enrolled in a randomized control trial of an experimental chemotherapy treatment.

METHODS

*Participants:* Participants consist of 525 patients enrolled in a randomized control study by the Eastern Cooperative Oncology Group.  In order to be eligible, patients had confirmed stage IIIB or IV stage non squamous cell lung cancer, no brain metastases, no previous chemotherapy treatment, and no history of malignant disease (with exception of certain skin and cervix types).

*Study Design:* Patients were randomly assigned to either the control condition, traditional chemotherapy treatment of paclitaxel plus cisplatin (n=125), or to one of two dose versions of the experimental treatment condition, etoposide plus cisplatin (n=250).  Patients’ quality of life was assessed at four timepoints: baseline, 6 weeks, 12 weeks, and 26 weeks.  If quality of life measures were not collected at any time-point, the reason for the missing observation was noted.  Reasons included: refusal, language, staff unavailable, staff oversight, patient felt too ill, staff felt patient was too ill, and patient expired.

*Primary Outcome*:

*Summary health-related quality of life score* (QOL) is an index score, 1 to 100, based on the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and consisting of subscales of: physical well-being, functional well-being, and lung cancer-related concerns.  The FACT-L also included social well-being and emotional well-being subscales that did not factor into the summary QOL index score. Higher values indicate higher quality of life.

*Measured Auxiliary Variables:*

In addition to the primary outcome (QOL), several auxiliary variables were also measured including: duration of survival (days), maximum CTC toxicity, prior radiation treatment, metastatic disease symptoms, systemic symptoms, and number of cycles of chemotherapy. While some of these measures such as prior radiation treatment were collected at baseline, most of these measures such as duration of survival, maximum CTC toxicity, and number of cycles of chemotherapy were collected during and after the trial period.

*Statistical Methods*:

For primary analysis, we examine QOL over the three post-baseline time periods using a mixed-effects model.  We allow a random-intercept for each patient and an unstructured covariance.  The random intercept allows for differences between patients at baseline.  We could not find any a priori information to justify a linear or constant change in QOL with time.  Therefore, we modeled the mean response for each treatment group at each time-point (means model).   Estimating the means at each time-point does increase the model degrees of freedom (d.f.), but with only 3 post-baseline time-points and 525 cases we did not feel that the reduction on power (from an increase in 5 model d.f.) would justify the strong assumption a constant time effect.

*Sensitivity Analyses*:

Our primary analysis utilizes maximum likelihood estimation methods (ML) and is therefore unbiased providing  1) the sample is large enough, and 2) the model is correctly specified.  Since this is a random control trial, the model should not require the specification of additional variables satisfying the latter condition.  However, due the large portion of missing outcomes the asymptotic assumption may not be met.  Therefore, we repeat the above analysis with multiple imputation (MI) and compare these results to the primary analysis estimates.  Furthermore, by imputing values for the missing observations based on their auxiliary measures, we may use MI model to evaluate the missing at random assumption of the primary analysis.   Differences between the primary and multiple imputation model estimates would suggest that data are missing not at random.

We used MI by Markov-Chain Monte-Carlo (MCMC).  We included all auxiliary variables with a correlation with the outcome above 0.15.  This set of variables included all of the QOL sub-scores (physical well-being, functional well-being, emotional well-being, social well-being, and additional concerns) as well as ECOGS performance status, systemic symptoms, number of cycles started, and an indicator for < 6 cycles and PD.  We also included an indicator for treatment arm. Since many of the missing observations were due to death we included survival duration in days in the imputation model.  We imputed 2,000 data sets by sampling every 100th iteration of the MCMC chain after a burn-in of 20,000 iterations.  We selected initial parameter estimates via expectation maximization (EM) performed on 300 bootstrap samples of the data to create over-dispersed values.  We then estimated the treatment effect at each time-point separately for each of the 2,000 imputed data sets with a generalized linear model and treatment effect as a sole predictor.   We combined results and estimated the treatment effect and standard error using Rubin’s rules.

RESULTS

Examination of raw mean QOL scores shows that among those observed, QOL did not appear to decline across time (Table 1). However when using the ML estimate, which is robust when data are missing at random and accounts for patient specific differences at baseline, decline from baseline QOL is clearly observed (Table 2). Among the experimental group, QOL is significantly lower at 12 weeks (-3.15, CI -5.29 to -1.01, p=.003) and at 26 weeks (-5.17, CI -7.64 to -2.68, p<.0001).  Among the control group, QOL has significantly declined only by the 26th week (-4.74, CI .91 to 8.57, p=.01).

*Table 1. Mean quality of life score at each time-point, by experiment arm, and number of observations at each timepoint (n, out of 525 patients).*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **QOL at:** | **Control** | | **Experimental** | |  |
| *Time* | *Mean (SD)* | *n* | *Mean (SD)* | *n* | *Total n* |
| **baseline** | 64.84 (15.82) | 168 | 65.88 (16.21) | 332 | 500 |
| **6 weeks** | 64.63 (15.42) | 103 | 65.63 (15.96) | 251 | 354 |
| **12 weeks** | 65.92 (17.49) | 80 | 65.32 (15.32) | 190 | 270 |
| **26 weeks** | 65.32 (15.39) | 53 | 64.64 (15.63) | 129 | 182 |

*Table 2. Estimated change in QOL score from baseline QOL, by experiment arm (unadjusted means model)*

|  | **Time** | **Estimate** | **SE** | **DF** | **t Value** | **p-value** | **Lower CL** | **Upper CL** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Control** | **6 weeks** | -2.47 | 1.51 | 778 | -1.63 | 0.10 | -5.43 | 0.50 |
|  | **12 weeks** | -1.95 | 1.65 | 778 | -1.18 | 0.24 | -5.19 | 1.29 |
|  | **26 weeks** | -4.74 | 1.95 | 778 | -2.43 | 0.02\* | -8.57 | -0.91 |
| **Experimental** | **6 weeks** | -1.35 | 0.99 | 778 | -1.36 | 0.17 | -3.29 | 0.59 |
|  | **12 weeks** | -3.15 | 1.09 | 778 | -2.89 | 0.003\* | -5.29 | -1.01 |
|  | **26 weeks** | -5.17 | 1.26 | 778 | -4.09 | <.0001\* | -7.64 | -2.69 |

In primary analysis, the direct comparison between the control arm and the experimental arm at each time-point shows no significant difference between treatment groups at any time-point (Table 3A) The difference between experimental and control groups for the estimated post-baseline average of all time-points was 0.95 (CI -2.04 to 3.94) and was also not significant.

*Table 3. Estimated difference between experimental arm minus control arm at each timepoint, and for the estimated average of post-baseline assessments. A.) Unadjusted Mixed Model Estimate B.) Multiple Imputation Estimates*

|  | **A. Unadjusted Mixed Model Estimates** | | | | **B. Multiple Imputation GLM Estimates** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Expt - Control** | **Estimate** | **SE** | **Lower** | **Upper** | **Estimate** | **SE** | **Lower** | **Upper** |
| **baseline** | 1.12 | 1.53 | -1.88 | 4.12 | 0.82 | 1.52 | -2.16 | 3.80 |
| **6 weeks** | 2.24 | 1.79 | -1.28 | 5.76 | 2.18 | 1.78 | -1.31 | 5.67 |
| **12 weeks** | -0.08 | 1.98 | -3.96 | 3.80 | -0.35 | 2.05 | -4.37 | 3.66 |
| **26 weeks** | 0.69 | 2.32 | -3.86 | 5.24 | 2.56 | 2.46 | -2.26 | 7.38 |
| **post-baseline avg** | 0.95 | 1.52 | -2.04 | 3.94 |  |  |  |  |

*Sensitivity Analysis*

Examination of the documented reasons for missing observations show that at the 26th week there is substantial missing observations due to death or severe illness, with the control arm missing 42% and the experimental arm missing 31% of observations due death or illness.

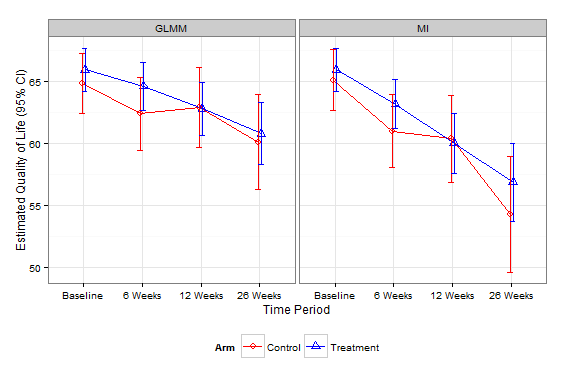
For the multiple imputations calculation, an evaluation of the MCMC chains suggested that parameter distributions were stable and well mixed after the burn-in period.

When examining the difference between treatment and control arms at each time-point, results from the MI sensitivity analysis are similar to those from the primary analysis (Table 3A, 3B).  After MI, we found no significant differences (alpha= 0.05) between the QOL in the experimental and control arms.  The estimates of these differences are very similar to the primary unadjusted GLMM model estimates, with the exception of 26 weeks, where the estimated difference between the experimental arm and control arm is larger in the MI model, though still non-significant (fig1, Table X, A & B: unadj. GLMM = .69, CI  -3.86 to 5.24 ; MI model= 2.56, CI  -2.26 to 7.37).

However, estimates from imputation show a steeper decline in QOL over the course of the trial (Figure 1B) for both controls and experimental arms as compared to the unadjusted estimates (Figure 1A).   At the 26 week time-point, the estimated mean QOL for controls was 60.1 ( 56.3 to 63.9 CI) in the primary analysis and 54.3 (49.6 to 59.0 CI) in the sensitivity analysis, and for the experimental group estimates were 60.8 ( 58.3 to 63.3 CI) for primary and 56.9 (53.7 to 60.0 CI).

*Figure 1. Estimated QOL score means at each timepoint, by arm. For A) primary analysis, unadjusted mixed model (GLMM) and B.) sensitivity analysis, multiple imputation model (MI).*

A. B.



DISCUSSION

Our primary analysis suggests that QOL declined over time for both groups.  This decline was significant at 12 and 26 weeks for the experimental group, and was significant for the control group at 26 weeks.  However, we did not find any significant differences in QOL between the treatment and control arms of this trial at any individual time-point or over the average of post-baseline QOL measures.

The results of the multiple imputation sensitivity analysis did not change our results with regard to QOL in the treatment versus control groups.  However, the trend in QOL over time did appear to decline at a higher rate in the MI estimates.  This suggests that missing observations were systematically biased towards cases with lower QOL and therefore missing not at random.  Omitting those results appears to have biased the primary analysis estimates of QOL higher.  Although we did not formally test for a difference between these estimates, the 95% confidence interval for the MI estimate does not overlap the unadjusted model estimate.

The sensitivity analysis suggests that the loss of observations may have inflated the estimated QOL scores for both groups, especially in the later time-points when groups have experience substantial observation loss due to death and illness.  If one treatment group were to experience greater observation losses due to death or severe illness, we may be limited in the ability to detect differences between this group and its comparison group when only analyzing observed data.  This potential limitation is highlighted when comparing the primary model results versus the sensitivity model results for the control group, which had a larger percentage of death and illness-related missing observations: the control group show a steeper mean QOL decline from 12 weeks to 26 weeks and a larger estimated difference between treatment minus control QOL.