Biost 518
Applied Biostatistics II

Scott S. Emerson, M.D., Ph.D.
Professor of Biostatistics
University of Washington

Lecture 7:
Case Study

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Lecture Outline

- Projects
- Case Study
  - Scientific Background
  - Materials and Methods
    - Source of Data
    - Statistical Methods
  - Results
  - Discussion

Projects

Timeline

- Feb 20: Assignment of Groups/Topics
  - Cerebral Atrophy
  - Inflammatory Markers
- Mar 3: Initial Report Due
- Mar 8: Referees' Report Due
- Mar 15: Final Report Due

Cerebral Atrophy

- Questions:
  - Who tends to have cerebral atrophy?
    - Is atrophy associated with other variables?
  - Is atrophy associated with mortality?
  - Do measures of atrophy provide information beyond more cheaply measured variables?
  - Is cerebral atrophy a symptom or a disease?
    - May be just more discussion of previous analyses

Inflammatory Markers

- Questions:
  - Who tends toward higher inflammation?
    - What other variables are associated with markers?
  - Is inflammation associated with mortality?
  - (Long term vs short term prediction)
  - (Effect modification by Sex)
  - Is inflammation a symptom or a disease?
    - Do markers provide information beyond other measured variables?

Goals of Case Study

Case Study

- "Use of cytosine arabinoside and total body irradiation as conditioning for allogeneic marrow transplantation in patients with acute lymphobalstic leukemia: a multicenter survey"
  - Weyman, et al., Bone Marrow Transplantation 11: 43-50, 1993.

Observational Study

- Compare the disease free survival in patients treated with a particular conditioning regimen to historical reports of other treatments
  - Major analysis issues
    - Summary measures of survival distribution to report
    - Selection of groups to use as strata for estimation of outcomes
    - Comparison to historical reports of other therapies

Goals of Case Study

- Illustrate approach to a data analysis problem in which data driven analyses play a major role
  - Approach to the data
  - Issues to address during analysis of time to event data
  - Data driven identification of groups for analysis
  - Presentation of results

Scientific Background

Scientific Background

- Bone marrow transplantation in acute lymphoblastic leukemia
  - Patients who had relapsed or were at high risk of relapse were commonly recipients of bone marrow transplantation
    - Eliminate leukemia from the bone marrow
      - high doses of chemotherapy and total body irradiation
    - Infuse healthy bone marrow from suitable donor

Scientific Background

- Conditioning regimens
  - Previous standard conditioning regimen was cyclophosphamide and total body irradiations
  - Interest in cytosine arabinoside (ara-C) due to its penetrance into central nervous system and efficacy in reinducing patients whose leukemia had relapsed

Scientific Background

- Question of interest
  - Was the experience with ara-C any better than that previously reported with the cytoxan conditioning regimen?

Materials and Methods

Source of Data

- Survey of 14 centers using ara-C as a conditioning regimen
- 222 patients treated between 1981 and 1989

Scientific Classification of Data

- (Classification by statistician)
  - Demographics (age, sex, race)
  - Presentation of ALL at diagnosis (date, WBC, immunophenotype)
  - Conditioning regimen (ara-C dose, other agents, irradiation)
  - Bone marrow transplantation (date, remission status, donor information)
  - GvHD prophylaxis
  - Outcome (relapse, cause of death)

Materials and Methods: Table 1

- Descriptive statistics on available data to provide information on materials and methods
  - Missing data (pervasive in such studies)
    - Especially race, cell count, duration of disease
    - ?Quality of cooperation among centers
  - Location: Mean, median, percentages of binary data
  - Spread: Standard deviation, frequency tables, range

Table I Patient characteristics

Covariate	*Available cases*	*Frequency (%)*	*Mean (SD)*	*Median (range)*
Age (years)	210		13.3 (9.3)	10.7 (0.5–45.7)
0–2		2.4		
2–7		27.1		
7–11		21.0		
11–16		19.5		
16–25		19.0		
25–46		11.0		
Male sex	211	66.7		
White race	156	91.0		
Cell count at diagnosis ($\times 10^9$/l)	129		51.3 (75.2)	16.4 (1–365)
1–10		38.0		
10–20		18.6		
20–40		13.2		
40–160		20.9		
160–400		9.3		
Immunophenotype	166			
Null		36.1		
CALLA		25.3		
T cell		17.5		
B cell		12.0		
Pre-B		9.0		
Duration of disease (years)	150		2.9 (2.5)	2.3 (0.0–17.9)
Disease status	207			
REM 1		12.1		
REM 2		57.5		
REM 3+		15.5		
REL 1[a]		6.8		
REL 2+		8.2		
Donor matching status	192			
Sibling, full match		91.1		
Sibling, partial match		5.7		
Non-sibling, partial match		3.1		
Myeloablative regimen[b]				
Ara-C 36 g/m^2	213	81.7		
Alkylating agents	208	3.4		
TBI dose	213		11.6 (1.2)	12.0 (6.0–15.8)
Fractionated TBI	213	92.5		
RT boosts	208	17.8		
GVHD prophylaxis[b]				
Cyclosporin A	213	30.0		
Methotrexate	213	54.9		
Prednisone	208	29.3		
T cell depletion	208	10.1		
ATG	208	9.6		

[a]Includes failed inductions
[b]Some patients received more than one therapy

Statistical Task

- Provide estimates of distribution of clinical outcomes
  - Essentially a one sample problem: All subjects received ara-C
  - However, may want to make description within groups defined by important prognostic variables
    - Readers will have to compare results to those reported in the literature or in their practice

Summary Measure

- Choice of summary measure for outcome
  - Interested in relapse and death
    - Disease free survival
  - Variable time of follow-up: Censored data
  - Choices:
    - Quantiles (e.g., median)
    - Survival probabilities at fixed points in time
      - 100 days indicative of toxic death from BMT
      - 1, 3, or 5 year survival probabilities for clinical relevance, comparisons

Predictors

- Definition of groups for presentation of estimates
  - Identify strongest predictors of survival
    - Allows more precision of estimates
    - Allows comparability with other studies
  - Methods
    - Most statistically significant predictors
    - Form of models to allow comparability

Statistical Methods

- Description of statistical methods
  - Methods for descriptive statistics: Kaplan-Meier
    - Necessary because nonstandard at the time
  - Methods for model building
    - Analysis methods: Proportional hazards
      - Interpretation
    - Model building
      - Selection of variables
      - Validity of assumptions
  - Missing data

Results

Organization of Results

- Presentation builds to conclusions
  - Dispense with potential nuisance covariate
    - Calendar year
  - Finding important predictors of survival
    - Univariately
    - Multiple regression model
  - Presentation of estimates within major strata
  - Comparison to previously reported results for other regimens

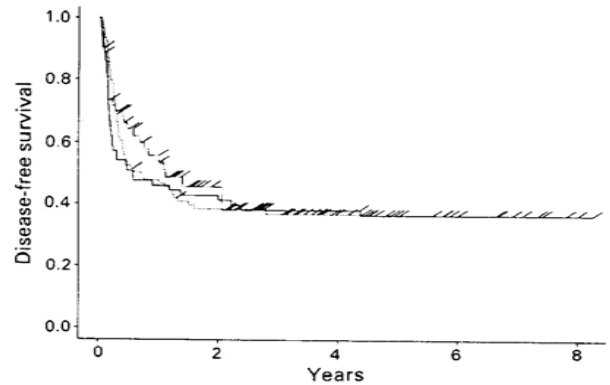

Figure 1 Unadjusted disease free survival by year of BMT. (—) 1981–84 ($n = 63$); (····) 1985–86 ($n = 89$); (– ··· –) 1987–89 ($n = 61$).

Model Building: Univariate First

- Table II: Present statistically significant univariate predictions
  - Overall test for trend based on continuous model
  - Descriptive estimates within strata
    - Strata chosen independent of outcome
    - Reference group chosen to allow sufficient precision for comparisons
  - Space constraints suggest that nonsignificant variables could be examined only in Table III
- Figures display Kaplan-Meier curves by strata
  - Note depiction of censored data

Table II Unadjusted hazard ratios and disease-free survival probabilities

Covariate	*n*	*Hazard ratio*	*95% CI*[a]	*Disease-free survival probabilities*[b]			
				100 day	1 year	3 year	*p*
Overall				0.67 ± 0.06	0.50 ± 0.07	0.38 ± 0.07	
Age (years)							0.0003
0–2	5	0.90	0.21, 3.83	0.80 ± 0.35	0.80 ± 0.35	0.40 ± 0.58	
2–7	57	1.00	baseline	0.80 ± 0.10	0.71 ± 0.13	0.58 ± 0.14	
7–11	44	1.44	0.79, 2.62	0.77 ± 0.13	0.57 ± 0.15	0.45 ± 0.16	
11–16	41	2.66	1.51, 4.66	0.54 ± 0.16	0.41 ± 0.15	0.27 ± 0.14	
16–25	40	3.13	1.80, 5.46	0.55 ± 0.15	0.30 ± 0.14	0.24 ± 0.13	
25–46	23	2.69	1.43, 5.06	0.61 ± 0.20	0.30 ± 0.18	0.21 ± 0.17	
Cell count at diagnosis ($\times 10^9$/l)							0.028
1–10	49	1.00	baseline	0.80 ± 0.12	0.63 ± 0.13	0.37 ± 0.14	
10–20	24	0.69	0.32, 1.45	0.75 ± 0.18	0.65 ± 0.20	0.60 ± 0.20	
20–40	17	1.26	0.63, 2.53	0.71 ± 0.22	0.41 ± 0.23	0.34 ± 0.23	
40–160	27	0.70	0.35, 1.41	0.81 ± 0.15	0.62 ± 0.19	0.57 ± 0.19	
160–400	12	2.47	1.19, 5.10	0.50 ± 0.28	0.17 ± 0.21	0.17 ± 0.21	
Disease status							0.005
REM 1	25	1.00	baseline	0.80 ± 0.16	0.59 ± 0.20	0.54 ± 0.20	
REM 2	119	1.35	0.71, 2.56	0.70 ± 0.08	0.53 ± 0.09	0.42 ± 0.10	
REM 3	32	1.48	0.71, 3.12	0.69 ± 0.16	0.53 ± 0.17	0.37 ± 0.18	
REL 1[c]	14	2.46	0.98, 5.21	0.64 ± 0.25	0.36 ± 0.25	0.21 ± 0.21	
REL 2+	17	3.53	1.61, 7.71	0.35 ± 0.22	0.24 ± 0.21	0.18 ± 0.18	
Donor matching status							0.0001
Sibling, full match	175	1.00	baseline	0.68 ± 0.07	0.50 ± 0.07	0.41 ± 0.08	
Sibling, partial match	11	1.26	0.59, 2.72	0.73 ± 0.27	0.52 ± 31	0.26 ± 0.30	
Non-sibling, partial match	6	6.59	2.80, 15.53	0.17 ± 0.30	0.00 ± NA	0.00 ± NA	

[a]CI = confidence interval
[b]Kaplan-Meier estimates of DFS with range of 95% confidence interval
[c]Includes failed inductions

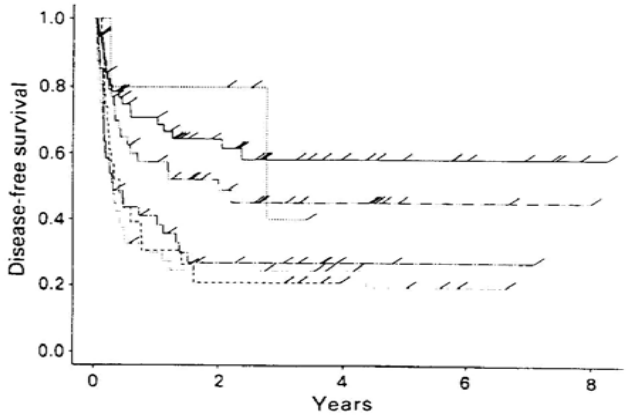

Figure 2 Unadjusted disease-free survival by age at BMT. (····) 0–2 ($n = 5$); (—) 2–7 ($n = 57$); (– ··· –) 7–11 ($n = 44$); (– – –) 11–16 ($n = 41$); (··· ···) 16–25 ($n = 40$); (- - -) 25–46 ($n = 23$).

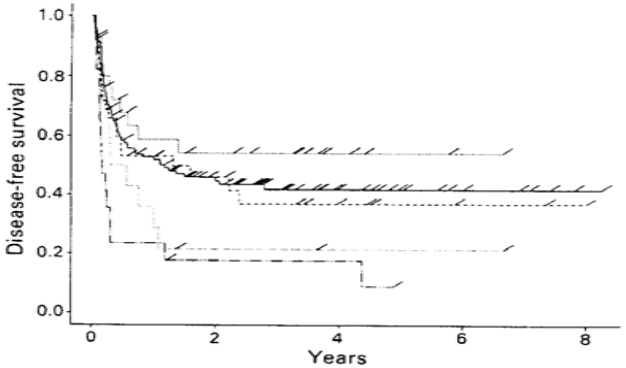

Figure 3 Unadjusted disease-free survival by disease status at BMT. (····) REM 1 ($n = 25$); (—) REM 2 ($n = 119$); (- - -) REM 3+ ($n = 32$); (··· ···) REL 1 ($n = 14$); (– ··· –) REL 2+ ($n = 17$).

Model Building: Multivariate

- Table III: Estimates of association adjusted for "final model"
  - Selection of variables (and form of variables) for final model based on
    - Statistical significance
    - Need for relatively few strata
    - Ability to compare with the literature
  - Obvious data-driven aspect to choice of final form of variables
    - Should be careful about believing any thresholds dividing the strata

Table III Multivariate proportional hazards model for disease-free survival

Covariate	*n*[a]	*Hazard ratio*	95% *CI*[b]	*p value*
Variables included in final model:				
Final model	195			
Age > 11		2.35	1.58, 3.50	< 0.0001
Not in remission		2.63	1.61, 4.30	0.0001
Non-sibling donor		2.64	1.13, 6.14	0.025
More than 1 remission		1.77	1.05, 2.96	0.031
Covariate effects adjusted for final model:				
Date of BMT (year)	195	0.99	0.89, 1.10	0.853
Male sex	193	0.98	0.64, 1.49	0.920
Black race	140	1.20	0.58, 2.51	0.625
Cell count at diagnosis > 160×10^9/l	118	2.01	0.99, 4.08	0.052
Immunophenotype	150			0.421
Null		1.00	baseline	
CALLA		1.23	0.70, 2.17	
T cell		1.55	0.84, 2.86	0.421
B cell		1.38	0.68, 2.78	
Pre-B		0.67	0.25, 1.80	
Duration of disease (years)	135	0.93	0.86, 1.00	0.063
Myeloblative regimen				
Ara-C 36 g/m^2	195	1.02	0.64, 1.62	0.937
Alkylating agents	190	0.23	0.03, 1.68	0.148
TBI dose	195	0.94	0.81, 1.08	0.358
Fractionated TBI	195	0.95	0.49, 1.85	0.889
RT boosts	190	0.88	0.54, 1.44	0.615
GVHD prophylaxis				
Cyclosporin A	195	1.08	0.76, 1.63	0.703
Methotrexate	195	0.88	0.60, 1.30	0.527
Prednisone	190	1.11	0.72, 1.70	0.638
T cell depletion	190	1.55	0.89, 2.71	0.129
ATG	190	1.69	0.97, 2.96	0.066

[a]Cases used in analysis
[b]CI = confidence interval

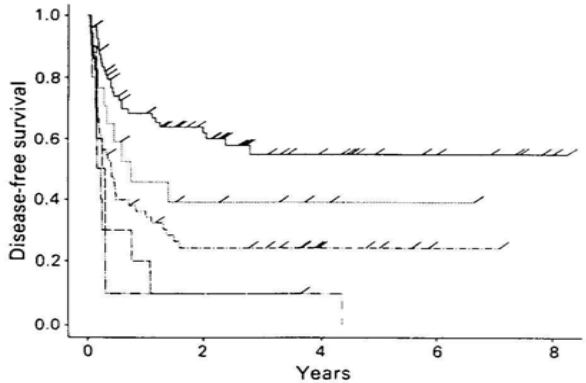

Figure 4 Disease-free survival by risk groups of final model. (—) age < 11, sibling, REM 2+ ($n = 80$); (····) age > 11, sibling, REM 1 ($n = 17$); (– – –) age > 11, sibling, REM 2+ ($n = 57$); (– – –) age > 11, sibling, REL 1 ($n = 10$); (– ··· –) age > 11, sibling, REL 2+ ($n = 10$).

Discussion

- Table IV: Direct comparison with previously reported results for cyclophosphamide insofar as possible from literature
  - Provide estimates of survival and relapse to match patient populations and time frames

Table IV Comparison of this study results with previously reported probabilities of disease-free survival and relapse following BMT (sibling donor) using other regimens

Risk group	*Reported probabilities from other studies*			*Comparable[a] probabilities from this study*		
	n	*DFS[b]*	*Relapse[c]*	*n*	*DFS*	*Relapse*
Barrett *et al.* (1982) (Ref 20) (CY-TBI, 3-year survival)						
Age < 26, REM 1+	19	0.48 ± 0.33	0.42 ± 0.38	146	0.47 ± 0.08	0.28 ± 0.10
Woods *et al.* (1983) (Ref 17) (CY-TBI, 3 year survival)						
Age < 24, REM 2,3	15	0.33 ± 0.24	0.43 ± 0.29	122	0.44 ± 0.10	0.29 ± 0.11
Sanders *et al.* (1987) (Ref 19) (CY-TBI, 3-year survival)						
Age < 18, REM 2	57	0.40 ± NA	0.42 ± NA	85	0.50 ± 0.12	0.27 ± 0.13
Brochstein *et al.* (1987) (Ref 18) (CY-TBI, 5 year survival)						
Age < 20, REM 2	31	0.64 ± 0.18	0.13 ± 0.14	89	0.49 ± 0.12	0.28 ± 0.13
Age < 20, REM 3	12	0.42 ± 0.27	0.25 ± 0.25	25	0.37 ± 0.20	0.33 ± 0.28
Age < 20, REL 1+	16	0.23 ± 0.22	0.64 ± 0.31	22	0.27 ± 0.19	0.41 ± 0.28
Bordigoni *et al.* (1988) (Ref 7) (CY-TBI, 3 year survival)						
Age < 17, REM 1	34	0.79 ± 14	0.10 ± 0.10	10	0.70 ± 0.28	0.00 ± NA
Blume *et al.* (1989) (Ref 8) (Etoposide-TBI, 5-year survival)						
Age 16–41, REM 1	50	0.61 ± NA	0.14 ± NA	13	0.43 ± 0.28	0.36 ± 0.33
Age 3–48, REM 2, 3	49	0.45 ± NA	0.41 ± NA	133	0.42 ± 0.09	0.31 ± 0.10
Age 5–54, REL 1+	51	0.19 ± NA	0.64 ± NA	27	0.09 ± 0.15	0.80 ± 0.30

[a]DFS and relapse probabilities computed for comparable risk group using data from this study
[b]Estimated probability of DFS with range of 95% confidence interval
[c]Estimated probability of relapse with range of 95% confidence interval

Discussion

- Limitations of study
  - Observational aspect of study
  - Confounding by treatment center
  - (Data driven aspect of selecting strata)