Hematological Malignancies

Discussion of posters 1069PD and 1070PD

Essential parameters relevant to clinical practice:

Prognostic factors/index

Endpoints

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Disclosure slide

- Advisory board member for Amgen, Merck Serono, Takeda Millenium, Boehringer-Ingelheim
- Dose steering committee member for Fresenius Biotech

Prognostic factors: Variables that can account for some of the heterogeneity in the expected course and outcome of a disease

Important for:

- Patient care: select treatment, predict outcome, assess outcome of therapeutic intervention
- Research: prognostic stratification, design future studies
- Cancer control programs: plan resource requirements, introduce clinical practice guidelines, monitor results

Classification of prognostic factors

- **Tumour related**: directly related to the presence of the tumour or its effect on the host (pathology, anatomic extent, tumour biology)
- **Host related**: inherent demographic characteristics (age, gender, ethnicity, performance status, comorbidity, immune status)
- **Environment related**: operate external to the patient (health care policies, access to care, socioeconomic status)

IPI for aggressive lymphomas

- Developed with available data from2031 pts. treated 1982-97 in 16 centres in the US, Western Europe and Canada
- Risk factors: age > 60, LDH↑, > 1 extranodal site, stage III or IV, PS ≥ 2
- Problems:
  - May not be the best or most relevant parameters (no biologic factors)
  - Determined with outdated treatments
  - Mixes tumour related and host related factors
  - Determined in western industrialized countries

Predicting early outcomes of high grade non Hodgkin's lymphoma: A comparative study of International Prognostic Index (IPI) with Subjective Global Assessment (SGA).

Vikas Ostwal, Reena Nair, Priyanka Bagayatkar, Preeti Pawasker, Ravi T., Bhausaheb Bagal, Manju Sengar, Navin Khattry, Hari Menon, Sumeet Gujral, Mohandas KM.

Tata Memorial Centre, Mumbai, India.

STUDY DESIGN & STATISTICAL ANALYSIS

- Prospective observational study at a tertiary cancer centre in India after approval by the IRB.
- Total 495 patients, registered in lymphoma clinic from January 2010 to December 2010, were eligible.
- All were screened for malnutrition using a validated modified subjective global assessment (SGA) tool.
- Explanatory and out come data collated by chart review.
- Response evaluation by Revised response evaluation criteria
- Out come variables were stratified as bivariate variable (Yes/No).
- Data was analyzed using SPSS ver. 16 and EpiInfo™ ver.3.5.3.
- Association of explanatory variables such as SGA and IPI risk scores with outcome variable(CR and 1 year OS) were estimated using univariate and multivariate analysis.
- Survival was estimated using Kaplan Meir method

Association of IPI and SGA for important outcomes

IPI Group (# patients)	L (n=133)	LI (n=95)	HI (n=91)	H (n=70)	P value
Complete response	112 (84%)	63 (67%)	46 (50%)	27 (38%)	0.000
Overall survival at 1-Yr	119 (90%)	73 (77%)	60 (65%)	30 (42%)	0.000
Tumor progression	16 (12%)	20 (21%)	34 (37%)	33 (47%)	0.000
Relapse after CR	2 (1.8%)	4 (6.3%)	0 (0%)	4 (14%)	
SGA group (# patients)	A (n=188)	B (n=129)		C (n=72)	P value
Complete response (%)	157 (84%)	72 (56%)		19 (26%)	0.0000
Overall survival at 1-Yr	171 (91%)	82 (63%)		29 (40%)	0.0000
Tumor progression	17 (9%)	43 (33%)		43 (60 %)	0.0000
Relapse after CR	6 (3.8%)	2 (2.78%)		2 (10.5%)	

Risk factors associated with failure to achieve complete response

Risk groups	Univariate analysis			Multivariate Analysis			p value
	OR	95%	C.I.	OR	95%	C.I.	
SGA-Score (B/A)	4.653	2.784	7.777	3.974	2.274	6.943	0.0000
SGA-Score (C/A)	13.59	7.116	25.98	9.381	4.492	19.587	0.0000
IPI Group (LI/L)	1.845	1.013	3.358	1.407	0.720	2.746	0.3169
IPI Group (HI/L)	4.090	2.281	7.336	2.484	1.267	4.868	0.0080
IPI Group (H/L)	5.301	2.816	9.978	2.781	1.305	5.926	0.0081
Private care (Y/N)	0.307	0.185	0.506	0.424	0.235	0.763	0.0042
Rituximab used (Y/N)	0.374	0.231	0.605	0.348	0.197	0.616	0.0003

Present study by Ostwal et al.

- 401 pts. with aggressive lymphoma evaluated prospectively
- Malnutrition assessed by Subjective Global Assessment (SGA)
- SGA-scores correlated with IPI variables
- SGA-scores independent predictors of RR, 1-year OS, and disease progression
- Is SGA significantly better than IPI?
- Does SGA-scores significantly increase the prognostic information when added to IPI?
- Does the prognostic value of IPI hold outside the western industrialized countries?

Endpoints

- Aim of treatment: provide clinical benefit in the patient population
- Evidence that the chosen primary endpoint can provide a valid and reliable measure of clinical benefit is needed
- Acceptable primary endpoints (EMA guidelines): cure rate, overall survival, progression/disease free survival
- The magnitude of the treatment effect on all relevant outcome measures forms the basis for the benefit-risk assessment

Overall survival (OS)

- Objective (particularly important in open label studies) and easy to measure
- Demonstrating differences in OS may be unattainable due to:
  - Optional cross-over at time of tumour progression
  - Active next-line therapies
  - Requires extensive follow-up

Surrogate endpoints needed

- EMA: progression free survival (PFS, time to tumour progression or death from any cause) may be primary endpoint, but OS should be secondary endpoint
- But: if major differences in toxicity are expected OS is the appropriate endpoint

The Relationship between Progression-free Survival and Overall Survival in Chronic Lymphocytic Leukemia: a literature-based analysis

Beauchemin C,

Johnston JB, Lapierre ME, Aissa F, Lachaine J.

Objectives and Methods

Objectives

- The surrogacy of progression-free survival (PFS) and time to progression (TTP) for overall survival (OS) is not validated in all cancer settings.
- The main objective of this study was to evaluate the relationship between median PFS/TTP and median OS in the context of chronic lymphocytic leukemia (CLL) using a trial-based approach.

Methods

- A systematic review of the literature was conducted using the **PICO** method:
  - **P**opulation consisted of patients with CLL
  - **I**nterventions and **C**omparators (when applicable) were standard therapies for CLL
  - **O**utcomes were median PFS/TTP and median OS.
- Two independent reviewers screened titles, abstracts, and full papers for eligibility, and then extracted data from selected studies.
- Correlation coefficient was calculated to assess the relationship between median PFS/TTP and median OS.
- Subgroup correlation analyses were also conducted according to characteristics of selected studies such as line of treatment and type of treatment under investigation.

Results and Conclusion

Results

- Among the 1,263 potentially relevant studies identified by the literature search, 23 articles were included.
- The mean number of patients included in these studies was 118 patients (min: 30, max: 724).
- On average, median PFS/TTP was 14.0 months (sd=12.4) and median OS was 35.0 months (sd=31.2).
- Results of the correlation analysis indicated that median PFS/TTP is highly correlated with median OS, with a Spearman's correlation coefficient of 0.813 ($p \leq 0.001$).
- A significant correlation between median PFS/TTP and median OS was observed in the second-line and subsequent-line therapies, but not in the first-line setting.

Conclusion

- The present results demonstrate a very strong correlation between median PFS/TTP and median OS in the context of CLL, which reinforce the hypothesis that PFS/TTP would be adequate surrogate endpoints for OS in this cancer setting.

Surrogate endpoints

- Able to predict the effect of treatment on the true endpoint after observation of the treatment effect on the surrogate
- A claim of surrogacy requires stronger conditions than a mere correlation between the surrogate and the true endpoint
- Evaluate:
  - The correlation between endpoints (individual level)
  - The correlation between treatment effects on these endpoint (trial level)
  - The latter assumes greater importance in the validation process.

Progression free survival: an attractive endpoint

- Available earlier than overall survival
- Less influenced buy competing causes of death
- Not influenced by second line treatment

BUT:

- In open label trials, ascertainment of PFS may be subject to bias
- Validation requires large datasets of pts. randomly assigned to treatments and in whom both the surrogate and the true endpoints have been measured
- Hazard ratio for the treatment effect should be compared for the two endpoints.

Conclusion

- Parameters used for clinical research and clinical practice need careful evaluation
- Statistical methods for evaluating and comparing parameters are not always straightforward