Survival by first-line treatment type and timing of progression among follicular lymphoma patients

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About Me

Background:
- MSc in Mathematical statistics (2009)
- PhD in Medicine (2018)
- Applied biostatistician - cancer epidemiology with a focus on lymphoma

Today:
- 40% as researcher at the Clinical Epidemiology Unit, Karolinska Institutet
- 60% as lead scientist at War On Cancer (https://waroncancer.com/)
Lymphoma - malignancies that arise in lymphoid tissue
Lymphoma - more than 70 diseases

- Diffuse large B-cell lymphoma: 35%
- Mantle cell lymphoma: 6%
- Burkitt lymphoma: 1%
- Aggressive B-cell lymphoma, uns: 2%
- T/NK-cell lymphoma: 8%
- NHL uns: 7%
- Follicular lymphoma: 17%
- Lymphoplasmacytic lymphoma: 7%
- Marginal zone lymphoma: 6%
- Indolent B-cell lymphoma, uns: 4%
- Small lymphocytic lymphoma: 4%
- Hairy cell leukemia: 2%
- Other: 1%

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Follicular lymphoma

- Follicular lymphoma (FL) is a mostly indolent malignancy.
- Some patients require treatment, whereas others do not (watch and wait).
- Usually not considered curable, but more of a chronic disease.
- Clinical outcome (prognosis) is highly variable.
- POD24 (progression of disease within 24 months) has been suggested as an important prognostic marker of overall survival (OS).
- Most research on POD24 have been in clinical trial settings and with patients treated with immunochemotherapy.
Prognostic value of POD24 validation in follicular lymphoma patients initially treated with chemotherapy-free regimens in a pooled analysis of three randomized trials of the Swiss Group for Clinical Cancer Research (SAKK)

Summary

The relapse of follicular lymphoma (FL) within 24 months (POD24) of chemoimmunotherapy has been associated with poor survival. We analyzed a pooled dataset of three randomized trials including FL patients with advanced disease, conducted by the Swiss Group for Clinical Cancer Research (SAKK). Overall, POD24 was observed in 27% of 318 patients, but rate variance among studies suggested that the rituximab schedule might affect POD24 rate. POD24 was associated with lower 10-
POD24 in FL patients is well studied

**Progression of disease within 24 months of initial therapy (POD24) detected incidentally in imaging does not necessarily indicate worse outcome**

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**ABSTRACT**

Progression of disease within 24 months of initial therapy (POD24) has previously been identified as a predictor of reduced overall survival (OS) for patients with follicular lymphoma (FL). Here we describe the relapse of follicular lymphoma (FL) within 24 months (POD24) of chemotherapy-maintenance therapy has been associated with poor survival. We analyzed a pooled dataset of three randomized trials including FL patients with advanced disease, conducted by the Swiss Group for Clinical Cancer Research (SAKK). Overall, POD24 was observed in 27% of 318 patients, but rate variance among studies suggested that the rituximab schedule might affect POD24 rate. POD24 was associated with lower 10-
Progression of disease within 2 years (POD24) is a clinically relevant endpoint to identify high-risk follicular lymphoma patients in real life

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Abstract
Follicular lymphoma (FL) is an indolent non-Hodgkin’s lymphoma with heterogeneous outcomes. Progression or relapse of FL within 2 years (so-called POD24) after diagnosis is associated with a poor outcome for patients treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone) in clinical trials. POD24 needs further validation before it can be used as a relevant endpoint to assess treatment efficacy. In the present retrospective monocentric study, we investigated the predictive value of POD24 in a cohort of grade 1-3 FL patients treated in our institution (Olveira Medical University).
However, this measure has some inbuilt issues

- Patients are followed from the “risk-defining event” which makes the time scale different for progressed and progression-free patients
- Only progressions within 24 (not 25, 26, ...) months are considered
- Progression-free patients who die before 24 months are excluded from analyses

(Casulo C et al, J Clin Oncol 2015)
What is the impact of POD, and timing thereof, on OS among FL patients treated with immunochemotherapy versus immunotherapy only?
Population-based study

**FL patients in the Swedish Lymphoma Register 2007-2014 (n=2,079)**

- **896 patients excluded**
  - No 1st line treatment (n=412), grade 3B (n=72), limited stage and/or RT treated only (n=346), transformation prior to first line treatment (n=66)

**Cohort of stage II-IV patients receiving 1st line systemic treatment (n = 948)**

- **R-chemo**
  - n=519 (55%)
    - R-CHOP n=308 (59%)
    - BR n=150 (29%)
    - R-CVP n=45 (9%)
    - R-FC n=16 (3%)

- **R-single**
  - n=273 (29%)

- **Other**
  - n=156 (16%)
An illness-death modelling approach

PF, progression-free; POD, progression of disease
Modelling and predictions

- Modelling of transition rates:
  - Flexible parametric survival models
  - Treatment group (R-chemo, R-single, other), time-varying effects
  - Adjusting for time of entry to POD (semi-Markov)
  - Package merlin

- Prediction of transition probabilities:
  - 5-year OS conditional on time of POD/PF
  - Package multistate
Modelling transition rates with merlin

// Transition 1
stmerlin tr2 tr3 /// main effects
    if _trans==1 /// fl -> dead
        , dist(rp) df(3) /// flexible parametric model
tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m1

// Transition 2
stmerlin tr2 tr3 /// main effects
    if _trans==2 /// fl -> POD
        , dist(rp) df(3) /// flexible parametric model
tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m2

// Transition 3
stmerlin tr2 tr3 /// main effects
    _t0 /// semi-Markov
        if _trans==3 /// POD -> dead
        , dist(rp) df(3) /// flexible parametric model
tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m3
range ptime 0 10 100
gen tvar5 = 5 + ptime

// Predict the conditional 5-year overall survival
forvalues ptindex = 1/100 {
    cap drop temptime
    gen temptime = tvar5[‘ptindex’] in 1

    predictms,transmat(tmat) /// specify transition matrix
        models(m1 m2 m3) /// specify models
        from(1 2) /// starting states
        at1(_t0 ‘=ptime[‘ptindex’]’ tr1 1) /// R-chemo treated patients
        at2(_t0 ‘=ptime[‘ptindex’]’ tr2 1) /// R-single treated patients
        at3(_t0 ‘=ptime[‘ptindex’]’ tr3 1) /// Patients treated with other
        timevar(temptime) /// prediction time
        ltruncated(‘=ptime[‘ptindex’]’) /// entry time
        probability /// transition probability
}
5-year OS by time of POD/PF: R-CHEMO vs R-Single

Conditional 5-year overall survival for FL patients treated with R-chemo (left) and R-single (right). The dashed line represents POD/PF-24.
Conclusions

- Progression mainly before, but also after 24 months, is associated with a worse 5-year overall survival among immunochemotherapy treated patients.

- This inferior survival remained for patients progressing at least within four years after treatment initiation.

- Among patients selected for immunotherapy only, progression of disease did not have a strong effect on the 5-year overall survival.
Thank you and some references below

