Is molecular remission the goal in first line therapy of all patients with indolent non-Hodgkin lymphoma?

Debate: YES position

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Conflict of Interest: nothing to disclose
Prognostic factors in FL

• Clinical (FLIPI-2, disease response)
• GEP signatures
• Tumor macrophages and infiltrating regulatory T cells
• Persistence of molecular disease

novel and accurate biomarkers are urgently needed
Some *practical* issues

- Definition of minimal residual disease (MRD) for CR patients
- Definition of molecular relapse
- Single, standardized PCR methodology is not currently in use
- Flow cytometry or PCR-based techniques to evaluate MRD (qualitative or quantitative approaches)
- Appropriate sampling is mandatory (PB or BM) to have reliable data. Optimal timing and frequency of PCR testing is still unknown
Some *philosophical* issues

Are MRD cells identical to the ones undergoing apoptosis during treatment? **Probably no**

Is there a role for microenvironment-mediated drug resistance? **Probably yes**

Is MRD a biomarker to deliver a more appropriate therapy or to avoid ineffective or expensive treatments? **Maybe in the near future!**
Open questions:

1. Can we routinely achieve molecular remission (MR) after treatment?

2. What is the clinical relevance of MR before and after Rituximab era?

3. Are there any clinical or biological factors that can be correlated with the MRD results?
Clinical situations where MRD has been tested:

1. Relapsed or refractory patients receiving autologous SCT

2. After chemotherapy or chemo-immunotherapy or RIT

3. After allogeneic SCT
Influence of complete response achievement during first-line therapy in the pre-Rituximab “era”

-536 FL patients (stage II-IV) -treated at diagnosis
-Median follow-up 15 yrs

In vitro purging of Bone Marrow Grafts

Figure 3. Actuarial Probability of Disease-free Survival after Autologous Bone Marrow Transplantation in 114 Patients with B-Cell Non-Hodgkin's Lymphoma.

"Negative" denotes the patients in whom PCR did not detect residual lymphoma cells after purging, and "positive" the patients in whom PCR did detect residual disease.

Up-dated results of autologous BMT in FCL from DFCI and SBH

Rohatiner AZS et al, J Clin Oncol 2007

In vitro purged BM

Median follow-up 13.5 years
Molecular monitoring of MRD in follicular and mantle cell lymphoma treated with high-dose CT and PBPC autografting

- **n = 30** advanced-stage disease (FL = 21; MCL = 9):
  - tumor marker in 90% patients: bcl2 or heavy-chain genes
  - clinical CR: in all evaluable FL and 6 of 9 MCL

  PCR negativity of PBPC and/or BM harvests: FL 68% (13 of 19), MCL 12% (1 of 8)

  - molecular follow-up on 14 patient: 7 received PCR-negative harvests and maintained negativity (median follow-up: 25.5 months)

- **A molecular marker to monitor MRD** was obtained in most FL and MCL

- **HDS regimen provided PCR-negative PBPC and/or BM harvests** even from patients with BM disease

  Autograft with at least one PCR-negative harvest is associated with prolonged remission.
MRD status influences the clinical outcome after autologous SCT in indolent lymphomas: long-term follow-up

DFS according to the PCR status of PBPC stem cell harvests

DFS according to post-transplant molecular status

Corradini P et al, JCO 2004
The clinical significance of molecular response in follicular lymphomas (FL)

- n = 194 of 236 patients with FL had Bcl-2/IgH seen between 1988 and 1995; chemotherapy according to the stage of FL

- follow-up: samples of BM and PB after every 3-4 cycles during the first year and every 4-6 months thereafter

Results:

1. at different time-points the molecular response rates progressively increased and were strongly correlated with FFS

2. the molecular response within the first year and the pretreatment serum b2-M were independent prognostic factors for FFS
The clinical significance of molecular response in indolent follicular lymphomas

PCR neg: 76%

PCR pos: 38%

\[ p = < 0.001 \]
Addition of Rituximab to front-line conventional chemotherapy

• **Advantage:**
  – Impressive ability to improve molecular remission (MR) rate (about 50% with CHOP)

• **Disadvantage:**
  – Relatively short observation time
  – About 20% of relapse rate in patients in MR
Monitoring of minimal residual disease after CHOP and rituximab in previously untreated FL patients

- $n = 128$ FL with Bcl-2/IgH PCR pos in PB or BM

- Treatment: 6 CHOP $\rightarrow$ if CR/PR + PCR pos: eligible for Rituximab (n = 76)

- Study end point:
  1. Evaluate the efficacy of Rituximab to induce PCR negativity in BM and PB in patients PCR pos in CR or PR after CHOP
  2. Evaluate the clinical activity of the sequence CHOP-R therapy

Follow-up on BM and PB at 12, 28 and 44 weeks after baseline. The study confirmed the clinical activity of rituximab and documented the clinical activity of the sequential administration of CHOP followed by rituximab.
Monitoring of minimal residual disease after CHOP and rituximab in previously untreated FL patients

FFR of PCR neg after CHOP without ritux

FFR after rituximab

PCR neg 57%

PCR pos 20%

n = 128

PCR neg after CHOP = 41

THE GITMO PHASE III TRIAL: 2000-2005

**RITUXIMAB**-supplemented HDS  
(Rituximab was given with an in vivo purging intent)

versus

**RITUXIMAB**-supplemented CHOP  
(CHOP and Rituximab were sequential not combined: CHOP-R)

**MAIN FEATURES:**

- multicenter randomized: 136 pts  30 Centers
- poor risk aaIPI and IIL criteria
- primary endpoint: EFS (crossover allowed)
- stratification according to histological grade
- molecular monitoring as secondary end-point
GITMO TREATMENT PLAN
Phase III trial in Follicular Lymphomas

arm R-HDS

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2 APO 2 DHAP

G-CSF

hd-VP16

Rituximab

hd-Cy

Rituximab

MITO/L-PAM + Autograft

Rituximab

PBS harvest

arm CHOP-R

CHOP 1-3

CHOP 4-6

Rituximab

MOLECULAR ANALYSIS
Maintenance Rituximab (MR) after CVP prolongs PFS in untreated advanced indolent lymphoma: results of ECOG1496 study

Stage III-IV with responding or stable disease after CVP were randomly assigned to OBS or MR (4 weekly infusions every 6 months for 2 yrs).

Hochster H et al JCO 2009
(A) PFS for 311 evaluable indolent lymphoma patients randomly assigned to maintenance rituximab (MR; n = 158) or observation (OBS; n = 153).

(B) PFS for 228 evaluable FL pts randomly assigned to MR (n=115) or OBS (n=113).
Fig 2.

(A) OS for 311 evaluable indolent lymphoma patients randomly assigned to maintenance rituximab (MR; n = 158) or observation (OBS; n = 153).

(B) OS for 288 evaluable FL pts randomly assigned to MR or OBS.
Fig 3.

(A) PFS for 158 evaluable maintenance rituximab (MR) patients according to minimal (n = 89) or gross (n = 69) residual disease after cyclophosphamide, vincristine, and prednisone (CVP) therapy.

(B) PFS for 115 evaluable MR FL patients according to minimal (n=67) or gross (n=48) residual disease after CVP.
First-Line Indolent Trial (FIT) study design

Blood samples from 414 advanced FL pts were evalutaed using real-time PCR for bcl-2 rearrangements. Overall 90% converted to PCR-neg compared to 36% in the control group.

[Diagram of study design]

INDUCTION
First-line therapy with chlorambucil, CVP, CHOP, CHOP-like, fludarabine combination, or rituximab combination

CONSOLIDATION
Rituximab 250 mg/m² IV day -7 and day 0 + ⁹⁰Y-ibritumomab tiuxetan 14.8 MBq/kg (max 1,184 MBq) day 0

CONTROL
No further treatment

Start of Study
Random Assignment
CR/CRu or PR

NR PD
No inclusion

Fig 2. Number of bcl-2 polymerase chain reaction (PCR) -detectable cells over time in patients receiving yttrium-90 (90Y)-ibritumomab or no additional therapy.
Fig 3. Kaplan-Meier plots of progression-free survival according to peripheral blood bcl-2 polymerase chain reaction (PCR) status at random assignment.

Fig 4. Kaplan-Meier plots of progression-free survival in patients converting from bcl-2 polymerase chain reaction (PCR) -detectable to PCR-undetectable status after random assignment.
Conclusions

- MRD as a “routine biomarker”, not yet. But if we test MRD in CR patients we should use the information.
- Prospective trials including MRD to stratify treatment are necessary.
- In general MRD negativity correlates with a better outcome. Is there any patient who is cured?