LymphomaHub

DLBCL

Prognostic value of NK cell count on DLBCL outcomes following immunochemotherapy

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On 3 May 2019, Magdalena Klanova from Charles University, Prague, CZ, and colleagues, published results from phase III GOYA (NCT01287741) and GALLIUM (NCT01332968) trials in *Clinical Cancer Research*. This exploratory analysis in patients with non-Hodgkin lymphoma (NHL) sought to investigate the potential prognostic value of natural killer cell count (NKCC) in predicting patient outcomes following anti-CD20 immunochemotherapy.

Study design & baseline characteristics

- GALLIUM phase III trial design (N = 1202):
  - Patients had previously untreated, histologically confirmed, $CD20^+$ follicular lymphoma (FL), with an Eastern Cooperative Oncology Group (ECOG) 0–2, stage III-IV disease (or stage II with bulky disease)
  - Patients were treated with six or eight cycles of rituximab (R) or obinutuzumab (G) plus chemotherapy in the form of CVP (bendamustine, cyclophosphamide, vincristine, and prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
  - At the end of induction, responding patients received maintenance therapy with G or R every two months for two years, or until disease progression (PD) or study withdrawal
- GOYA phase III trial design (N = 1418):
  - Patients had previously untreated, histologically confirmed, $CD20^+$ diffuse large B-cell lymphoma (DLBCL), with an ECOG 0–2, and an International Prognostic Index (IPI) score ≥2
  - Patients were treated with eight 21-day cycles of CHOP
- Baseline NKCCs were identified as $CD3^-CD56^+$ and/or $CD16^+$ cells with flow cytometry from peripheral blood (PB) samples
- Analysis population:
  - Number of patients with an evaluable NKCC at baseline:
    - FL patients (GALLIUM trial; intention-to-treat population [ITT]): 88.5% (n = 1064)
    - DLBCL patients (GOYA trial; ITT): 90.8% (n = 1287)
  - Number of patients with evaluable baseline NKCC and cell-of-origin (COO):
    - DLBCL patients: 60.4% (n = 857/1418)
  - The cut-off between low and normal/high baseline PB NKCCs was evaluated in both FL and DLBCL patients with chi-square statistical analysis, eventually:
    - NKCCs were considered low if <100 cells/μl

- NKCCs were considered normal/high if ≥100 cells/μl
- Whole transcriptome RNA sequencing was performed in:
  - FL patients (GALLIUM): 19.6% (n = 236)
  - DLBCL patients (GOYA): 38.9% (n = 552)

Key findings

- PB NKCCs amongst all patients with evaluable NKCCs:

Baseline characteristic	**FL patients (GALLIUM)**	**DLBCL (GOYA)**
Median baseline PB NKCCs (range)	222 (13–3327) cells/μl	196 (5–1930) cells/μl
Patients with low PB NKCCs n, (%)	108 (10.2%)	255 (19.8%)

- PB NKCCs amongst DLBCL patients with evaluable NKCCs and COO:

Median baseline PB NKCCs by DLBCL COO subtype (range)	**Germinal center B-cell like (GCB)**	**Activated B-cell like (ABC)**	**Unclassified**	***P* value**
	186 (6–1659) cells/μl	200 (8–1930) cells/μl	167 (7–1715) cells/μl	-
Low baseline PB NKCCs (less < 100 cells/μl) n, (%)	83 (17.1%)	37 (26.4%)	54 (23.3%)	0.022

- In FL, patients with low baseline PB NKCCs had more frequent:
  - Extranodal disease
  - Elevated lactate dehydrogenase (LDH)
  - Higher FLIPI scores

    - Higher sum of products of diameter (SPD)
- In DLBCL patients with low baseline PB NKCCs had higher:
    - Ann Arbor disease stage
    - ECOG performance status
    - IPI score
    - SPD
- No association was observed between baseline PB NKCC levels and frequency of bone marrow involvement in patients with either FL or DLBCL
- Multivariate analysis showed that low baseline PB NKCC was independently associated with shorter PFS in DCBL and FL, and OS in FL.
    - Three-year PFS rate:
        - Low baseline PB NKCCs: FL=71.6%, DCBL=62.8%
        - Normal/high baseline PB NKCCs: FL=80.1%, DCBL=70%
        - Comparison: FL HR = 1.48; (95% CI, 1.02–14); *P* = 0.04, DCBL HR = 1.36; (95% CI, 1.01–1.83); *P* = 0.04
    - Three-year OS rate:
        - Low baseline PB NKCCs: 87.6%
        - Normal/high baseline PB NKCCs: 94.3%
        - Comparison: HR = 2.20; (95% CI, 1.26–86); *P* = 0.0058
    - Univariate analysis showed that low baseline PB NKCC was associated with shorter PFS independently of anti-CD20 antibody use:
        - FL patients:
            - R-based chemotherapy: HR = 1.19; (95% CI, 0.71–99)
            - G-based chemotherapy: HR = 2.06; (95% CI, 1.24–41)
        - DLBCL patients:
            - R-CHOP: HR = 1.47; (95% CI, 1.06–2.06)
            - G-CHOP: HR = 1.26; (95% CI, 0.90–1.77)
        - Low CD56 mRNA expression (as a continuous variable) was associated with shorter PFS (*P* = 0.043) in patients with DLBCL but not with FL (*P* = 0.0447)
        - No correlation was observed between baseline PB NKCCs and tumor NK cell gene markers in patients with FL (n= 201 evaluable patients; *P* = 0.46; *r* = 0.053) or with DLBCL (n = 508 evaluable patients; *P* = 0.25; *r* = 0.05)
        - No significant difference in PFS was observed between low and high tumor NK cell gene expression in patients with FL (multivariate analysis: HR = 0.84; [95% CI, 0.50–4]; *P* = 0.5) or DLBCL (multivariate analysis: HR = 1.31; [95% CI, 0.95–1.81]; *P* = 0.11)

Safety

- No significant difference was observed between the frequency of Grade 3–5 and infusion-related reactions (IRRs) in DLBCL patients with low *versus* normal/high baseline PB NKCC
- More Grade 3–5 events and serious infections were observed among patients with FL and low PB NKCC when compared to those with normal/high PB NKCC

Conclusions

The results of this exploratory analysis indicate that the number of PB circulating NK cells could act as a prognostic biomarker for FL or DLBCL patient outcomes and allow the development of novel combination treatment approaches tailored to the number of functional effector cells in NHL.

References

1. Klanova M. *et al*. Prognostic impact of natural killer cell count in follicular lymphoma and diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Clin Cancer Res*. 2019 May 3. pii: clincanres.3270.2018. DOI: 10.1158/1078-0432.CCR-18-3270 [Epub ahead of print].