Article

Predictive model for occurrence of febrile neutropenia after chemotherapy in patients with diffuse large B-cell lymphoma: a multicenter, retrospective, observational study

**Supplementary Material**

Table S1. Univariate analysis of factors associated with febrile neutropenia incidence during any cycle for patients treated with R-CHOP-like regimen

|  |  |  |  |
| --- | --- | --- | --- |
|  | Developed FN  during any cycle | Did not develop FN  during any cycle | p-value |
|  | n = 64 | n = 130 |  |
| Age ≥ 65 years | 47 (73%) | 91 (70%) | 0.62 |
| Sex: male | 38 (59%) | 71 (55%) | 0.53 |
| Comorbidity |  |  |  |
| Diabetes | 10 (16%) | 22 (17%) | 0.82 |
| Chronic kidney disease | 5 (8%) | 5 (4%) | 0.24 |
| Cardiac disease | 12 (19%) | 21 (16%) | 0.65 |
| Pulmonary disease | 2 (3%) | 2 (2%) | 0.46 |
| Malignancy | 8 (12%) | 16 (12%) | 0.97 |
| Baseline laboratory data |  |  |  |
| WBC < 3.5 × 109 /L | 7 (11%) | 15 (12%) | 0.9 |
| Hemoglobin < 12.0 g/dL | 33 (52%) | 59 (45%) | 0.42 |
| Platelet < 100 × 109 /L | 14 (22%) | 10 (8%) | 0.005 |
| ANC < 1.5 × 109 /L | 2 (3%) | 6 (5%) | 0.62 |
| ALC < 0.7 × 109 /L | 24 (38%) | 18 (14%) | < 0.001 |
| T-Bil > 1.0 g/dL | 9 (14%) | 18 (15%) | 0.92 |
| Albumin < 3.5 g/dL | 36 (58%) | 35 (27%) | < 0.001 |
| LD > 222 IU/L | 43 (68%) | 66 (51%) | 0.025 |
| CRP > 10 mg/dL | 5 (8%) | 5 (4%) | 0.29 |
| eGFR < 60  mL/min/1.73 m2 | 22 (34%) | 30 (23%) | 0.095 |
| sIL2R > 2000 U/mL | 37 (58%) | 35 (27%) | < 0.001 |
| Ann Arbor stage: Advanced (III–IV) | 49 (78%) | 59 (45%) | < 0.001 |
| Extranodal involvement | 41 (64%) | 61 (47%) | 0.025 |
| Bone marrow infiltration | 16 (25%) | 14 (11%) | 0.01 |
| Viral hepatitis status |  |  |  |
| Viral hepatitis | 18 (28%) | 22 (17%) | 0.07 |
| HCV | 9 (14%) | 4 (3%) | 0.004 |
| HBV | 13 (20%) | 20 (15%) | 0.39 |
| HBsAg + | 1 (2%) | 2 (2%) | 0.99 |
| anti-HBs + | 7 (11%) | 14 (11%) | 0.97 |
| anti-HBc + | 13 (20%) | 15 (12%) | 0.1 |

Abbreviations:

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FN, febrile neutropenia; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; LD, lactate dehydrogenase; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone with added rituximab; sIL2R, soluble interleukin-2 receptor; T-Bil, total bilirubin; WBC, white blood cell

Table S2. Univariate analysis of factors associated with febrile neutropenia incidence during the first cycle among patients in the salvage therapy group

|  |  |  |  |
| --- | --- | --- | --- |
|  | Developed FN  during the first therapy cycle | Did not develop FN  during the first therapy cycle | p-value |
|  | n = 9 | n = 43 |  |
| Age ≥ 65 years | 7 (78%) | 29 (67%) | 0.54 |
| Sex: male | 8 (89%) | 29 (67%) | 0.2 |
| Comorbidity |  |  |  |
| Diabetes | 1 (11%) | 3 (7%) | 0.67 |
| Chronic kidney disease | 0 (0%) | 4 (9%) | 0.34 |
| Cardiac disease | 1 (11%) | 4 (9%) | 0.87 |
| Pulmonary disease | 0 (0%) | 1 (2%) | 0.64 |
| Malignancy | 2 (22%) | 5 (12%) | 0.4 |
| Baseline laboratory data |  |  |  |
| WBC < 3.5 × 109 /L | 1 (11%) | 6 (14%) | 0.82 |
| Hemoglobin < 12.0 g/dL | 3 (33%) | 19 (44%) | 0.55 |
| Platelet < 100 × 109 /L | 2 (22%) | 6 (14%) | 0.53 |
| ANC < 1.5 × 109 /L | 1 (11%) | 0 (0%) | 0.027 |
| ALC < 0.7 × 109 /L | 3 (33%) | 9 (21%) | 0.42 |
| T-Bil > 1.0 g/dL | 0 (0%) | 8 (20%) | 0.17 |
| Albumin < 3.5 g/dL | 6 (67%) | 10 (24%) | 0.012 |
| LD > 222 IU/L | 7 (78%) | 31 (72%) | 0.73 |
| CRP > 10 mg/dL | 1 (12%) | 2 (5%) | 0.41 |
| eGFR < 60  mL/min/1.73 m2 | 2 (22%) | 7 (16%) | 0.67 |
| sIL2R > 2000 U/mL | 7 (78%) | 18 (42%) | 0.05 |
| Ann Arbor stage: Advanced (III–IV) | 9 (100%) | 35 (81%) | 0.16 |
| Extranodal involvement | 8 (89%) | 30 (70%) | 0.24 |
| Bone marrow infiltration | 2 (22%) | 12 (28%) | 0.73 |
| Viral hepatitis status |  |  |  |
| Viral hepatitis | 4 (44%) | 6 (14%) | 0.035 |
| HCV | 4 (44%) | 6 (14%) | 0.035 |
| HBV | 1 (11%) | 1 (2%) | 0.21 |
| HBsAg + | 0 (0%) | 2 (5%) | 0.51 |
| anti-HBs + | 2 (22%) | 4 (9%) | 0.27 |
| anti-HBc + | 3 (33%) | 3 (7%) | 0.024 |

Abbreviations:

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FN, febrile neutropenia; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; LD, lactate dehydrogenase; sIL2R, soluble interleukin-2 receptor; T-Bil, total bilirubin; WBC, white blood cell

Table S3. Univariate analysis of factors associated with febrile neutropenia incidence during any cycle among patients in the salvage therapy group

|  |  |  |  |
| --- | --- | --- | --- |
|  | Developed FN  during any cycle | Did not develop FN  during any cycle | p-value |
|  | n = 36 | n = 16 |  |
| Age ≥ 65 years | 25 (69%) | 11 (69%) | 0.96 |
| Sex: male | 27 (75%) | 10 (62%) | 0.36 |
| Comorbidity |  |  |  |
| Diabetes | 2 (6%) | 2 (12%) | 0.39 |
| Chronic kidney disease | 4 (11%) | 0 (0%) | 0.17 |
| Cardiac disease | 4 (11%) | 1 (6%) | 0.58 |
| Pulmonary disease | 0 (0%) | 1 (6%) | 0.13 |
| Malignancy | 5 (14%) | 2 (12%) | 0.89 |
| Baseline laboratory data |  |  |  |
| WBC < 3.5 × 109 /L | 7 (19%) | 0 (0%) | 0.058 |
| Hemoglobin < 12.0 g/dL | 16 (44%) | 6 (38%) | 0.64 |
| Platelet < 100 × 109 /L | 7 (19%) | 1 (6%) | 0.22 |
| ANC < 1.5 × 109 /L | 1 (3%) | 0 (0%) | 0.5 |
| ALC < 0.7 × 109 /L | 11 (31%) | 1 (6%) | 0.055 |
| T-Bil > 1.0 g/dL | 6 (18%) | 2 (12%) | 0.61 |
| Albumin < 3.5 g/dL | 12 (34%) | 4 (25%) | 0.51 |
| LD > 222 IU/L | 27 (75%) | 11 (69%) | 0.64 |
| CRP > 10 mg/dL | 3 (9%) | 0 (0%) | 0.24 |
| eGFR < 60  mL/min/1.73 m2 | 7 (19%) | 2 (12%) | 0.54 |
| sIL2R > 2000 IU/L | 21 (58%) | 4 (25%) | 0.026 |
| Ann Arbor stage: Advanced (III–IV) | 30 (83%) | 14 (88%) | 0.7 |
| Extranodal involvement | 26 (72%) | 12 (75%) | 0.83 |
| Bone marrow infiltration | 11 (31%) | 3 (19%) | 0.38 |
| Viral hepatitis status |  |  |  |
| Viral hepatitis | 7 (19%) | 3 (19%) | 0.95 |
| HCV | 7 (19%) | 3 (19%) | 0.95 |
| HBV | 2 (6%) | 0 (0%) | 0.34 |
| HBsAg + | 0 (0%) | 2 (12%) | 0.031 |
| anti-HBs + | 5 (14%) | 1 (6%) | 0.43 |
| anti-HBc + | 5 (14%) | 1 (6%) | 0.43 |

Abbreviations:

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FN, febrile neutropenia; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; LD, lactate dehydrogenase; sIL2R, soluble interleukin-2 receptor; T-Bil, total bilirubin; WBC, white blood cell

Table S4. Multivariate logistic regression analysis of risk factors associated with febrile neutropenia incidence during any cycle among patients treated with the R-CHOP-like regimen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  | n = 191 |
|  | Odds ratio [95% CI] | β coefficient [95% CI] | Score | p-value |
| ALC < 0.7 × 109 /L | 2.61 [1.18–5.75] | 0.96 [0.17–1.75] | 1 | 0.018 |
| Alb < 3.5 g/dL | 2.33 [1.16–4.67] | 0.85 [0.15–1.54] | 1 | 0.017 |
| Ann Arbor stage: Advanced (III–IV) | 3.32 [1.60–6.89] | 1.20 [0.47–1.93] | 1 | 0.001 |

Abbreviation: Alb, albumin; ALC, absolute lymphocyte count; CI, confidence interval; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone with added rituximab

Table S5. Bootstrap validation of the predictive model for febrile neutropenia occurrence during any cycle among patients treated with the R-CHOP-like regimen and comparison with the original model

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  | n = 191 |
|  | Logistic regression β coefficient [95% CI] | Bootstrapped β coefficient [95% CI] | Score |
| ALC < 0.7 × 109 /L | 0.96 [0.17–1.75] | 0.98 [0.12–1.79] | 1 |
| Alb < 3.5 g/dL | 0.85 [0.15–1.54] | 0.88 [0.15–1.54] | 1 |
| Ann Arbor stage: Advanced (III–IV) | 1.20 [0.47–1.93] | 1.21 [0.44–1.97] | 1 |

Abbreviation: Alb, albumin; ALC, absolute lymphocyte count; CI, confidence interval; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone with added rituximab

Table S6. Multivariate logistic regression of risk factors associated with febrile neutropenia incidence during the first cycle of chemotherapy among patients treated with the R-CHOP-like regimen, with a more detailed evaluation of the viral hepatitis status

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  | n = 191 |
|  | Odds ratio [95% CI] | β coefficient [95% CI] | p-value |
| ALC < 0.7 × 109 /L | 6.04 [2.39–15.23] | 1.80 [0.87–2.72] | <0.001 |
| sIL2R > 2000 U/mL | 3.03 [1.19–7.70] | 1.11 [0.17–2.04] | 0.020 |
| Extranodal involvement | 3.05 [1.08–8.57] | 1.11 [0.08–2.15] | 0.035 |
| HCV | 5.26 [1.28–21.69] | 1.66 [0.24–3.08] | 0.022 |
| anti-HBc + | 3.11 [1.00–9.68] | 1.13 [-0.001–2.27] | 0.050 |

Abbreviations: ALC, absolute lymphocyte count; anti-HBc, hepatitis B core antibody; HCV, hepatitis C virus; CI, confidence interval; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone with added rituximab; sIL2R, soluble interleukin-2 receptor![Chart, bar chart

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Figure S1. Differences in FN incidence between patients who received G-CSF during the first cycle of R-CHOP-like therapy and those who did not. Abbreviations: FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone with added rituximab

A graph of a person with a number of bars

Description automatically generated with medium confidence

Figure S2. Incidence rate of FN during the first cycle of chemotherapy for patients treated with the R-CHOP-like regimen based on each prediction score. Abbreviations: FN, febrile neutropenia; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone with added rituximab