Diffuse large B-cell lymphoma refractory to R-CHOP

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SUMMARY

Rituximab with cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) is the standard treatment for diffuse large B-cell lymphoma and is able to cure 50-60% of the patients. However, patients resistant to or in early relapse after R-CHOP have a very poor prognosis with a median overall survival of only six months, and very few patients have a long survival. Double-hit lymphoma (rearrangement *MYC* and *BCL2*) has a major risk of refractoriness, and more intense chemotherapy than R-CHOP is recommended. Early PET-CT could identify resistance to conventional chemotherapy. Intensification with autologous or allogeneic stem cell transplantation is recommended in case of a response to salvage regimen. New agents are expected and chimeric antigen receptor T-cell therapy is a very promising approach.

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INTRODUCTION AND DEFINITIONS

Major progress has been obtained in the treatment of diffuse large B-cell lymphoma (DLBCL) by the use of a monoclonal anti-CD20 antibody (rituximab) in association with the standard chemotherapy: cyclophosphamide, adriamycin, vincristine, prednisone (R-CHOP).[1]

With a ten-year follow-up, the disease-free survival (DFS) for complete response (CR) patients is 64.3%. For the whole population, event-free survival (EFS) and overall survival (OS) were 36.5% and 43.5%, respectively in a population of patients aged from 60-80 years old.[2]

Moreover, in a registry database, in British Columbia after R-CHOP, whatever the age, three-year (3y) EFS and OS were respectively 69% and 78%.[3]

R-CHOP is the standard of treatment for DLBCL for more than 15 years.

However, 20-25% of the patients will relapse either early (less than one year after diagnosis) or later. Five percent of the patients obtain a partial response (PR) with metabolic persistence of the disease, and 15-20% of the patients do not obtain any objective response.[4]

Definitions of resistant patients to R-CHOP are: (1) refractory patients do not respond (less than PR, stable disease or progressive disease) during treatment in first line (primary refractory) or during salvage regimen after relapse (secondary refractory); (2) early relapse is observed during the first year after diagnosis or after transplant; (3) late relapse occurred after more than one year.

Finally, 50-60% of DLBCL patients are cured by R-CHOP either after the first CR or in a second remission obtained by salvage regimen and autologous stem cell transplantation (ASCT). This salvage regimen is mainly effective in late relapse.[5] The prognosis of refractory and early relapse patients is extremely poor, and there is a medical unmet need for this population.

PROGNOSIS OF REFRACTORY PATIENTS

The international SCHOLAR-1 study is the first patient-level analysis of outcomes of refractory DLBCL patients from two large randomised trials, the CORAL study (LYSA group) and the Canadian LY.12, and two observational cohorts from the MD Anderson Cancer Center and Iowa/Mayo Clinic.[5-9]

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Refractory patients are either primary refractory after first line treatment (28%) or to salvage regimen (50%) or are in early relapse after ASCT (22%). A total of 636 patients were analysed.

This study demonstrates a very poor prognosis: the objective response rate to chemotherapy after refractory disease is only 26% (7% of CR), while the median OS is 6.3 months. Patients in CR have a better median survival (14.9 months) than those in PR (6.9) and those with no response (4.6). The median survival for patients receiving ASCT is 14.4 months versus 5.1 for those who do not receive ASCT.

The Eastern Cooperative Oncology Group performance status, stage, and International Prognostic Score are prognostic factors for survival.

Another publication from the Barcelona group on 206 refractory DLBCL patients reported the same bad results: median OS was 9 months.[10]

CHARACTERISTICS OF REFRACTORY PATIENTS

These following characteristics are more frequently encountered in refractory patients:

1. clinical factors related to patients: older age, male gender, presence of co-morbidities;
2. factors related to the tumour: high tumour volume, elevated lactate dehydrogenase, cell of origin, CD5 expression, genetic abnormalities (p53, double-hit mutation, double-hit expression);
3. factors related to host reactions: tumour microenvironment, C-reactive protein, performance status.[5]

However, except for double-hit mutations, no characteristic is sufficient to predict refractoriness and to guide to a different treatment than R-CHOP.

DOUBLE- OR TRIPLE-HIT MUTATIONS, *MYC* TRANSLOCATION ALONE, *BCL2* ALONE, DOUBLE EXPRESSOR PROTEIN

The majority of the patients resistant to R-CHOP presents mutations of *MYC* and *BCL2* or/and *BCL6* (double- [DHL] or triple-hit lymphoma [THL]).[11,12] These rearrangements are observed by fluorescence in situ hybridisation (FISH) immunofluorescence. These lymphomas are now recognised as a new category of high-grade B-cell lymphoma (HGBCL) with rearrangements of *MYC* and *BCL2* and/or *BCL6*.[13]

For these patients, treatment with R-CHOP is unsatisfactory: progression free survival (PFS) for R-CHOP is 7.8 months in DHL/THL versus 21.6 months (p=0.001) for other treatments.[14]

The patients with the poorest outcome have the highest level of *MYC* and *BCL2* expression as a result of translocation immunoglobulin (IG) loci.[15]

Patients with *MYC* translocations in the absence of *BCL2* translocations (single-hit) have a poor prognosis only if the translocation partner is an *IG* gene. *MYC-IG* patients have a shorter OS in comparison with *MYC*-negative patients (p=0.0002), but there is no difference in survival between *MYC*-non-IG and *MYC*-negative patients.[16]

Patients with *BCL2* translocations do not have a worse prognosis after R-CHOP.

Patients with hyperexpression of BCL2 alone (without MYC) have a poor prognosis only in germinal centre B-cell-like (GCB) but not in activated B-cell-like (ABC) DLBCL.[17]

Patients with double expressor proteins or dual-expressers (DEL) have in immuno-histochemistry a high expression of both the MYC and BCL2 protein, but without translocations. Predominantly seen in ABC DLBCL, the mechanism is largely related to NF-κB activation.[15] The prognosis is inferior to other DLBCL but better than DHL-HGBCL.[18]

COULD PET-CT ANTICIPATE RESISTANCE TO THERAPY?

Total metabolic tumour volume (TMTV) is obtained by summing the metabolic volumes of all local (l) nodal and extranodal lesions. The 41% maximum standardised uptake value (SUV) threshold method was used for MTVl computation.[19]

During initial staging, determination of TMTV is highly predictive for OS. In a multicentric study on 114 DLBCL patients, TMTV <550 ml predicted a better survival than TMTV >550 ml (p=0.0003).[20]

Many studies have demonstrated the prognostic value of early evaluation of response with a PET-scan. The first publications were reported in Belgium.[21,22] The assessment of response was obtained by visual method or semi-quantitative or SUV methods.[23,24]

The combination of TMTV and early PET evaluation improves sensibility of discrimination between a low or high risk of resistance.[25]

Moreover, in case of early PET-positivity, after two or four cycles of R-CHOP, intensification of treatment (carmustine, etoposide, cytarabine, and melphalan (BEAM) or Zevalin-BEAM) in positive patients could obtain the same prognosis as negative patients treated by conventional treatment.[26,27]

Despite that PET-positivity was not confirmed by biopsy, these studies suggested a role for intensification to overcome bad prognosis in these patients.

TREATMENT OF RELAPSE IN REFRACTORY PATIENTS

The classical management of relapse in DLBCL is to perform

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Diffuse large B-cell lymphoma patients resistant to rituximab with cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) or relapsing less than one year after diagnosis have a very poor prognosis with a median overall survival at six months and very few cures.**

2 **Double-hit lymphoma has a major risk of resistance to R-CHOP and should be treated more intensively.**

3 **Early PET-CT evaluation could identify resistant patients.**

4 **Chimeric antigen receptor T-cell therapy is a very promising approach.**

salvage chemotherapy followed, in case of response, by high-dose chemotherapy and ASCT.

The prospective international CORAL study tested two salvage regimens: rituximab, dexamethasone, high-dose cytarabine and cisplatin (R-DHAP) and rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) before BEAM + ASCT.[5] A total of 396 patients were enrolled, there was no significant difference between the two chemotherapy regimen.

However, a subsequent analysis showed an advantage for R-DHAP in patients with GCB phenotype.[28] For all patients, the objective response rate, CR, 3y EFS and 3y OS were respectively 63%, 38%, 31% and 50%, but for refractory patients, the 3y EFS and 3y OS were only 20% and 39%.

One American study on relapsing/refractory DHL and DEL patients showed inferior PFS after ASCT.[29] The four-year (4y) PFS was 28% for DHL *vs* 57% for non-DHL (p=0.013), and the 4y PFS was 48% for DEL *vs* 59% for non-DEL (p=0.049). The 4y OS was 25% for DHL *vs* 61% for non-DHL (p=0.002), and the 4y OS was 56% for DEL versus 67% for non-DEL (p=0.1). Five patients were DHL+DEL and none had PFS at four years.

However, patients in relapse after ASCT had a better prognosis if they received a second stem cell transplantation (SCT) as showed in the CORAL and the SCHOLAR-1 studies.[5,6,30]

European registry reported results of allogeneic SCT (alloSCT) after ASCT in 101 patients in relapse. The results were encouraging: 3y PFS was 41,7%; 3y OS was 53,8%. This population was highly selected and the relapse rate after alloSCT was significantly higher in refractory patients.[31]

Fenske published a study from the international database on 503 DLBCL patients who underwent transplantation after relapse post-ASCT.[32] The 3y PFS and OS were respectively 31% and 37%. Chemoresistance and early relapse post-ASCT were adverse prognostic factors.

DLBCL patients have a poor prognosis after alloSCT in comparison with other histological subtypes of lymphomas challenging the role of the graft-versus-lymphoma (GVL) effect in DLBCL.[33]

One argument in favour of the existence of the GVL effect is provided by a study analysing survival after transplantation according to the results of PET-CT before transplantation. Positivity of PET-CT means a bad prognosis but alloSCT provides better results than ASCT.[34]

Monotherapies in patients ineligible for high-dose therapy like gemcitabine, lenalidomide, bendamustine, ibrutinib, bortezomid and oxaliplatin obtained an objective response rate around 30% but with few CR and a very short PFS (around three months).

Blinatumomab, a bispecific T-cell engager antibody construct, was tested in a phase I study in 27 DLBCL patients. The response at the target dose in eleven patients was four CRs and two PRs.[35] The use of blinatumomab as a bridge before alloSCT was recently reported.[36]

Autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy was given to 101 patients from 111 refractory DLBCL patients enrolled. The results are very encouraging: ORR=82%, CR=54%. After a median follow-up of 15 months, 42% remains in response and 40% in CR; the OS at 18 months is 52%, two patients in CR received alloSCT. These results were favourably compared to SCHOLAR-1.[37]

FIRST LINE TREATMENT TO PREVENT REFRACTORINESS

Very few regimens have demonstrated superiority to R-CHOP. Adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone associated to rituximab (R-ACVBP) followed by sequential consolidation (high-dose methotrexate, etoposide, ifosfamide) has demonstrated superiority to R-CHOP in young patients with one adverse prognostic factor.[38]

However, this superiority appears only in ABC DLBCL, and

R-ACVBP was not directly compared with R-CHOP in DHL.[39] For DHL, the population at a higher risk of refractory disease, a meta-analysis showed that R-CHOP is inferior to many more intensive regimens in PFS but not in survival. Recently, Landsburg published a large study on 159 DHL patients who obtained a CR and were followed for outcome.[40] Patients treated with R-CHOP and in CR have an inferior relapse free survival and OS compared with patients treated by one of the intensive regimens R-hyperCYVAD, DA-EPOCH-R, R-CODOX-M/VAC. ASCT as consolidation does not improve results.

Consolidation of response after R-CHOP was tested with various molecules (rituximab, bevacizumab, enzastaurin, etc.) without improvement. Only lenalidomide improves PFS but not survival.[41] Several trials comparing R-CHOP with R-CHOP plus one new agent (lenalidomide, ibrutinib, venetoclax, etc.) are ongoing, but data are not yet available.

CONCLUSION

DLBCL patients refractory to R-CHOP have a very poor prognosis and represent a real therapeutic challenge.

Genetic studies are necessary to identify DHL. For these patients, intensive induction regimen such as R-ACVBP or DA-EPOCH-R are possibly preferable to R-CHOP.

For relapse/refractory patients, second line chemotherapy followed by ASCT is the preferred option in responding patients. For patients relapsing after ASCT, or not eligible for ASCT (age, not responding to second line chemotherapy), CAR T-cell therapy is a very promising approach.

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