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The Role of Autologous Stem Cell Transplantation in the Treatment of Diffuse Large B-cell Lymphoma in the Era of CAR-T Cell Therapy

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Abstract

For many years now and based on the results of the PARMA trial, relapsed Diffuse Large B-cell Lymphoma (DLBCL) is treated with salvage combination cytotoxic chemotherapy (most often platinum-based) followed by high dose myeloablative chemotherapy and autologous stem cell transplantation (auto-HCT). This approach has resulted in long-term disease free survival in about half of the patients. With the incorporation of rituximab in the upfront treatment (RCHOP), more patients with DLBCL are cured but there has been a signal of inferior outcomes with auto-HCT if DLBCL relapses. Nevertheless, a careful review of the literature still shows very good outcomes with auto-HCT for DLBCL with complete remission to salvage chemotherapy. For those who do not respond well to classic salvage other approaches are reviewed here including chimeric antigen receptor (CAR) T-cell therapy and treatment with antibody-drug conjugates (ADCs) as well as bispecific T-cell engagers (BiTEs). The outcome of auto-HCT after successful treatment with ADCs or BITEs is unknown. It is also unknown if CAR-T cell therapy should be reserved for those who have failed 2 lines of chemotherapy or it should be moved earlier. Finally, we review here the effects of Myc and bcl2 amplifications or translocations to the outcome of the auto-HCT. Some attempts to improve the salvage or conditioning regimens are mentioned. We also discuss the role of allogeneic stem cell transplantation (allo-HCT) in the paradigm of treatment for relapsed DLBCL.

Introduction

Relapsed/Primary Refractory Diffuse Large B-cell Lymphoma (DLBCL) when is sensitive to salvage chemotherapy can be cured with high dose chemotherapy and autologous stem cell rescue (auto-HCT). This strategy in the pre-rituximab trial of the PARMA group resulted in a higher event free survival (EFS) compared to the continuation of salvage chemotherapy alone (up to a total of 6 cycles of DHAP) among patients with high or intermediate grade Non-Hodgkin Lymphoma[1] (NHL) (5-year EFS 46% vs 12% favoring the auto-HCT group). It also translated to a superior 5-year overall survival (OS) of 53% vs 32% for those patients who received auto-HCT after high dose chemotherapy with BEAC (carmustine, etoposide, cytarabine and cyclophosphamide). It has to be noted that in this seminal trial the response to salvage chemotherapy based upon CT criteria, for relapsed DLBCL was 64% but for refractory DLBCL the response was only 21%.

Auto-HCT in the rituximab era

After rituximab addition to chemotherapy became standard for DLBCL, the most informative study for the applicability of the auto-HCT approach for relapsed or refractory (R/R) DLBCL is probably the CORAL study. In this trial,[2] patients with R/R DLBCL were first randomized to 3 cycles of either (R)-DHAP (dexamethasone, high dose cytarabine and cisplatin) or (R)-ICE (ifosfamide, carboplatin and etoposide). This trial included patients of both the pre-rituximab and the rituximab era. Patients without prior rituximab exposure had better response rates to salvage chemotherapy, by CT criteria, (83% for non-exposed vs 51% for rituximab-exposed, respectively). Patients with relapses occurring > 12 months after the start of initial treatment also had a higher response rate (88% vs 46%, favoring patients who relapsed later). The 3-year EFS as analyzed by intent to treat was only 21% for rituximab -experienced patients and only 20% for patients who relapsed within a year. Patients who were transplanted had a PFS of 40%.

A second randomization of post-transplant rituximab every 2 months vs no maintenance did not show any difference[3] to justify post-HCT rituximab in DLBCL patients. Although the 2 salvage regimens were equal in general, a post-hoc analysis showed possible superiority of (R)-DHAP for R/R DLBCL of germinal center (bio-CORAL study)[4] and there is evidence in other studies that RICE may be better in the activated B-cell subytpe.

A second study[5] (NCIC-CTG LY.12) randomized patients with relapsed/refractory lymphoma to DHAP or to GDP

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(gemcitabine-dexamethasone and cisplatin). Overall there was no difference in the response rate (GDP:45%, DHAP:44%), transplant rates (GDP:52%, DHAP:49%) or event-free survival. The CR rate was 14%, based upon CT criteria, in each group (almost 1/3 of all responses). GDP was less toxic, lead to less hospitalization and preserved better quality of life. In an intent to treat analysis, from 619 patients enrolled in both salvage regimens only 307 completed auto-HCT (49.5%). Only 26% of patients (equal between salvage regimens) achieved a 4-year EFS. The 4-year OS was 39%, also equal between the 2 salvage regimens. On further analysis, only 25% of all lymphoma patients with primary refractory disease responded to salvage (32% in the GDP and 18% in the DHAP group). With analysis starting at the time of transplantation the 4-year EFS was about 45% and the 4-year OS was 63%.

Both the NCIC-CTG LY.12 and the CORAL study results show that the group of early relapse (< 1 year) and primary refractory patients have a failure rate >80% with salvage chemotherapy and autologous stem cell transplant; however the transplanted patients still have a cure rate of 40%. Patients who attain CR2 after salvage chemotherapy fare better after auto-HCT, than those with < CR.

In the BMT-CTN 0401 trial[6] multivariate analysis for PFS, patients not in CR2 had a higher risk for an event (HR = 0.61) and the 2-year-PFS was better for the CR2 group irrespective of the arm (rituximab-BEAM or Bexxar-BEAM) of the transplant conditioning regimen.

So the critical questions are if a) we should offer transplant to only PET-negative patients after salvage and b) how we can improve on the transplant outcomes.

The significance of the post-salvage pet/ct scan

Sauter et al[7] reported on 129 patients with relapsed/refractory DLBCL who were transplanted in PR or CR. Patients with a Deauville score of 1 to 3 after salvage chemotherapy had an unprecedented 3-year PFS of 77%, whereas patients with a Deauville score of 4 had a 3-year PFS of 49%. Radiation therapy before or after the auto-HCT was allowed and in fact 42% of transplanted patients received XRT.

Armand et al[8] reported on 105 patients who had a PET scan after salvage chemotherapy for DLBCL and before their auto-HCT. Only 1/3 of patients with primary refractory disease had negative PET after salvage. Patients with a high secondary age-adjusted IPI (score of 2 or 3) also had lower chance for negative PET after salvage (35%) Overall 47% had a positive PET after salvage and 53% a negative PET. The 4-year PFS for patients who went to transplant with a positive PET was 32% whereas the respective PFS for patients who went to transplant with negative PET was 64%.

In a multivariate analysis for PFS, positive PET after salvage, (HR = 3.4), symptomatic relapse (HR = 2.4) and age >60 (HR = 2.1) were the unfavorable predictors. Interestingly, the secondary age-adjusted IPI was not predictive in the multi-variate analysis. A score was constructed. One point is given for each of the negative predictors (age, symptomatic relapse or positive PET after salvage). Patients with a score of 3 had a 4-year PFS of 0% while patients with a score of 2 did much better (4-year PFS:41%) and patients with low score (0–1) had an excellent PFS of 67% at 4 years.

Based on the data from the 2 previous studies, patients with Deauville score of 4 post-salvage should not be excluded from transplantation (Fig. 1). However the final decision should take multiple other factors. For example, patients with post-salvage positive PET will probably fail after auto-HCT if they have early relapse (within 1 year after the initiation of primary chemotherapy) or if they initially had failed to attain CR after induction or if they relapse with symptoms associated with high LDH. Biologic factors like double-hit or double-expressor lymphoma or Myc+ DLBCL also seem to be negative predictors unless the positive PET is restricted to one radiation field.

The case of primary refractory DLBCL

About 24% of DLBCL patients treated with R-CHOP are deemed chemorefractory.[9] The success rate of salvage chemotherapy with subsequent auto-HCT for chemosensitive disease in the rituximab era were informed by a retrospective review of 82 patients with primary refractory DLBCL to anthracycline +rituximab-based primary chemotherapy at MSKCC.[10] Based on

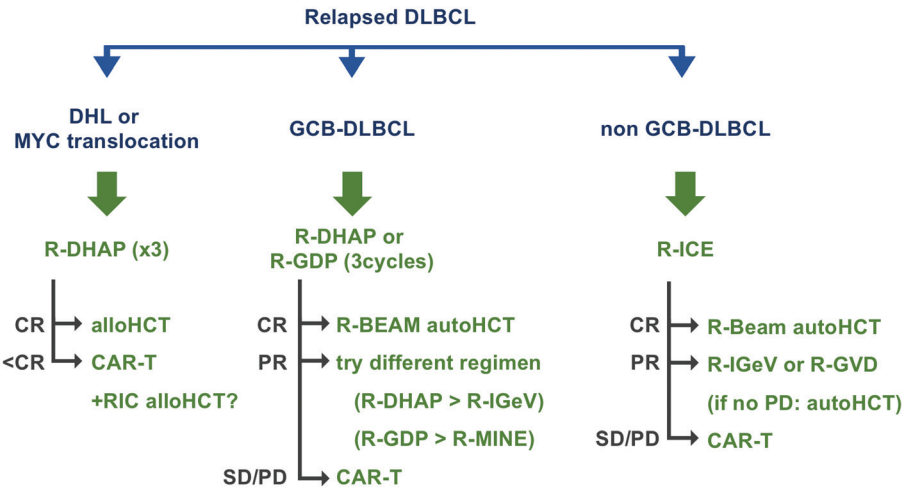

Figure 1. **Authors' algorithm for the treatment of relapsed DLBCL.**

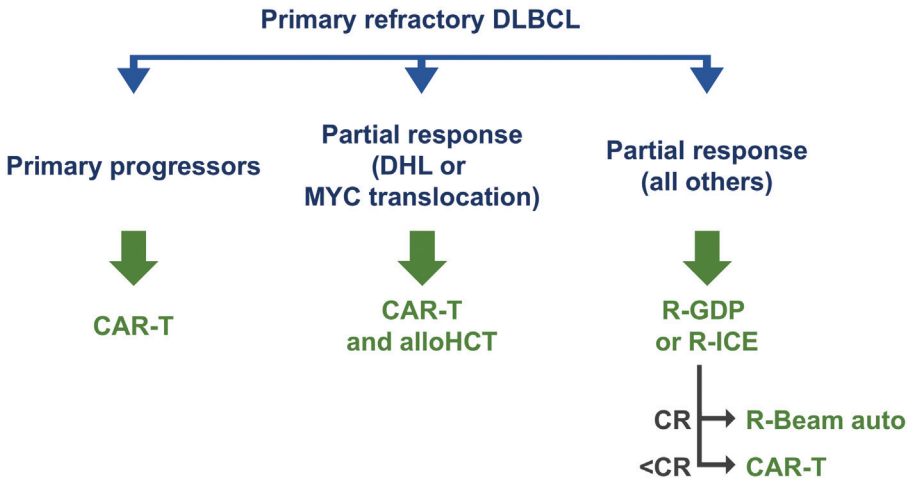

Figure 2. **Authors' algorithm for treatment of primary refractory DLBCL.**

this, patients should be divided to those who had a PR to primary chemotherapy and to those who did not respond to induction (Fig. 2). The 3-year PFS with salvage and auto-HCT was 49% in patients with PR to R-CHOP based chemotherapy while it was 17% for those who did not respond to induction. Approximately 67% of the initial partial responders to induction did respond to salvage (CR = 25%, PR = 43%) while between primary progressors the response to salvage was 40% (CR = 15%, PR = 25%). Overall, the 3-year PFS for all patients with primary refractory disease was 29%. Patients with a Deauville 4 after salvage had a 3-year PFS of only 30% while those with a Deauville 1 to 3 had much better 3-year PFS (67%). In a multivariate analysis, KPS < 80%, high LDH and primary progression to induction (marginally) were independent predictors of the outcome. Based on this report, primary progressors, refractory disease in a patient with KPS < 80% or high LDH are probably relative contraindications with salvage therapy and auto-HCT and patients should be moved to clinical trials. Also, it is questionable if primary refractory patients who do not have any of these 3 factors should be taken to transplant if they achieve only a PR to salvage with a Deauville score of 4 (since only 1/3 of those will stay in remission in the long term).

The impact of MYC and BCL2

More recently, insights in the molecular pathogenesis of DLBCL have identified certain groups with unfavorable prognosis. The best characterized is the "double-hit lymphoma" (DHL), now categorized by WHO as the provisional entity "High Grade B-cell Lymphoma with MYC, BCL2 and/or BCL6 rearrangements".[11] For DHL the most important determinator of prognosis is the intensity of first-line therapy, usually with dose-adjusted R-EPOCH, hyper-CVAD or Magrath regimen (Fig. 3). RCHOP is inferior to these regimens even if followed by consolidation with auto-HCT. For someone treated with intensive induction, consolidation auto-HCT is not recommended.[12] On the other hand, if a DHL relapses, salvage chemo followed by auto-HCT is not a very effective strategy.[13] Even if a DHL is deemed chemosensitive to salvage the 4-year PFS after auto-HCT is 28%. Double-expressor lymphomas (DEL: Myc+in >40% and Bcl2+

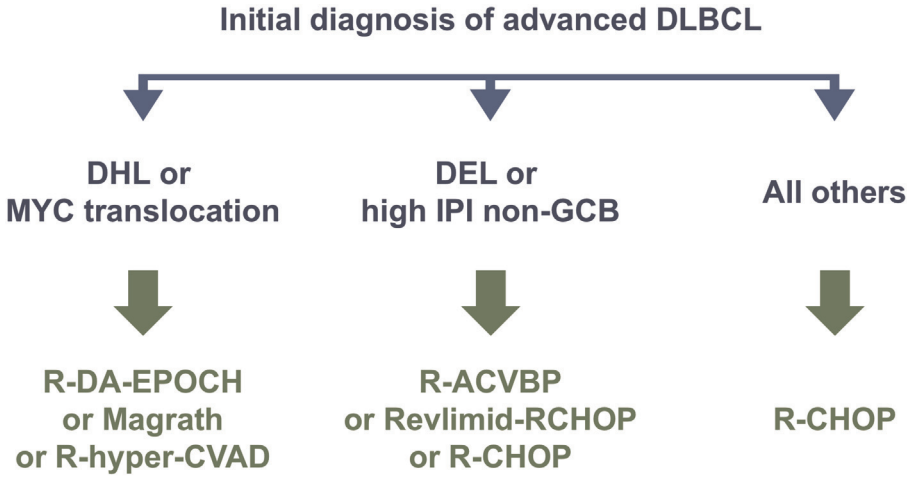

Figure 3. **Authors' algorithm for the initial treatment of DLBCL.**

in >50% of lymphoma cells on immunohistochemistry without the respective gene translocations) have better prognosis than DHL but worse than "generic" DLBCL. Relapsed DELs if they are chemosensitive and reach to auto-HCT, they have a 4-year PFS of 48% from the time of transplantation (compared to the 58% of 'generic" DLBCL).[13] This translates to the fact that a salvage attempt with chemo and auto-HCT is worthy in DELs (Fig. 1). Lastly, Myc-translocated DLBCL if they relapse within 6 months after primary therapy or if they are primary refractory do not do well with auto-HCT. Although half of these respond to salvage, they relapse after auto-HCT and the 2-year OS was 0% in one report.[14] In the same report, none of patients with early relapse (<6 month) or primary refractory DHL or triple-hit lymphoma enjoyed a prolonged PFS after auto-HCT. Similarly in the CORAL study, relapsed Myc-rearranged DLBCL could not be effectively salvaged with salvage chemotherapy and auto-HCT (3-year PFS:18% irrespective of the salvage).[15]

Salvage allogeneic HCT

Can allo-HCT overcome the negative prognosis of relapsed DHL or DEL? The answer is possibly shown in Fig. 1. If these patients go to allo-HCT with chemo-sensitive disease to allow time for Graft versus lymphoma, which may be difficult secondary to the growth rate of these lymphomas, they have similar outcomes to patients with 'generic' DLBCL who underwent allo-HCT. In a report from Harvard,[16] most patients had failed prior auto-HCT and they underwent reduced intensity conditioning without the use of ATG even in the matched unrelated setting to allow early GvL. The NRM at 4 years was 22% and the relapse rate 43%. The cGVHD at 1 year was 37% and 22% of patients developed geade II-IV acute GVHD with 10% of those being grade III-IV acute GVHD. The 4-year PFS for DHL was 30% and for DEL 40% which were not significantly different than the PFS of non-DHL, non-DEL DLBCL. This study showed that DHL may have relative chemoresistance but not immunoresistance. In the same study, older patients and patients with transformed indolent lymphoma fared surprisingly better, however the number of patients was small (N=78).

In general, patients with DLBCL who relapse after auto-HCT (Fig. 4) have a 31% chance of 3-year PFS after a subsequent allo-HCT (N=503, CIBMTR data),[17] and RIC allo is not inferior but less toxic and thus preferable in this setting. The outcome of an allo-HCT after previous auto-HCT is generally worse with chemorefractory disease at the time of allo-HCT, suboptimal KPS (<80%) and interval after auto-HCT of <1 year.

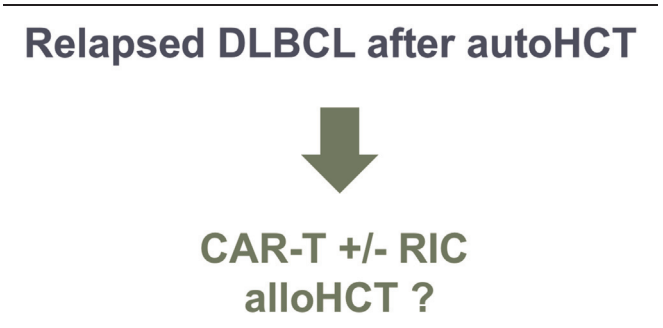

Figure 4. **Suggestion for the treatment of post auto-HCT relapse of DLBCL.**

Attempts to improve salvage therapy

In the salvage setting, multiple attempts have been made to improve outcome. Improvement has been tried with the addition of small molecules to immunochemotherapy. Lenalidomide added to RICE (RICER or R^2-ICE) has been associated with more cytopenias and uncertain benefit.[18] The addition of ibrutinib to RICE in a phase 1 trial showed that the combination was safe up to an ibrutinib dose of 840 mg/d and effective especially in GC-DLBCL where 8/9 patients achieved a metabolic CR.[19] The combination moved to the phase 2 investigation.

A question that remains unanswered is what to do if the PET scan shows a Deauville of 4 after 2 to 3 cycles of salvage chemotherapy. Should the patient be taken to auto-HCT or another "non-cross resistant" chemotherapy should be tested in an attempt to get to CR before auto-HCT?

It is uncertain if the outcome will be different but if someone wants to try that and has already given R-ICE salvage, two reasonable combinations are topotecan-paclitaxel-rituximab (TTR) and bendamustine-gemcitabine-vinorelbine (BeGeV). The first combination (TTR) was able to convert 45% of platinum-resistant DLBCL patients to transplantable. Among patients who received an auto-HCT, the 5-year OS was 63%. In an ITT analysis the 5-year PFS for all patients on protocol was 27%.[20] The second combination (BeGeV) has been mainly tried in Hodgkin Lymphoma with CR of 73% in refractory or relapsed disease but it can be used in DLBCL.[21]

Similar regimens borrowed by the Hodgkin Lymphoma literature like ifosfamide-gemcitabine and vinorelbine (IGeV)[22] or gemcitabine-vinorelbine and liposomal doxorubicin (GVD)[23] are salvage regimens that can be used after R-DHAP failure. All of these regimens are very myelosuppressive and is preferable that the stem cell collection is done before. In cases that only auto-HCT is a possibility and the patient cannot go to CAR-T therapy or allo-HCT or clinical trial, 2 cycles of any of these regimens is worthy to try to deepen the response before auto-HCT. It is important to note that the regimens BeGeV, IGEV and GVD have been mainly investigated in Hodgkin lymphoma and although they are composed of chemotherapeutic agents with activity against DLBCL, specific studies are warranted in DLBCL before thie activity is officially guaranteed.

Of note auto-HCT and RIC allo-HCT as a first transplant give approximately the same outcomes for chemosensitive relapse of DLBCL (4-year PFS: 48% vs 52% for auto and RIC allo-HCT respectively)[24] despite bias against the patients who go to allo-HCT (usually worse disease). The question which transplant is better after a Deauville of 4 to salvage chemotherapy is unknown as well. For example, outside of a clinical trial a patient with DEL and a Deauville of 4 after 2 cycles of RICE is not unreasonable to go to Flu-Mel allo-HCT after 2 cycles of gemcitabine-based chemotherapy.

Incorporating ADCs and BiTEs to salvage

Apparently, new effective treatments for salvage are warranted. Some of them are in clinical trials already. Polatuzumab vedotin is an antibody-drug conjugate (ADC) where monomethyl-auristatin E is conjugated to an antibody against CD79b which is a part of the B-cell receptor complex. The combination of bendamustine-polatuzumab vedotin-rituximab gave a metabolic CR of 40% in relapsed-refractory DLBCL in non-transplant eligible patients (Sehn et al, European Hematology Association Meeting, 2018). This is compared favorably to Bendamustine rituximab

(metabolic CR:15%).[25] Polatuzumab will be tested in combination with cyclophosphamide-doxorubicin-rituximab and prednisone in comparison to R-CHOP in the 1st line setting (POLARIX phase III trial). Other ADCs are targeting CD19 and include denintuzumab mafodotin[26] and loncastuximab tesirine (conjugated to a pyrrolobenzodiazepine dimer).[27] They both have shown CRs in the 20–30% range and some patients have stayed in CR for more than 1 year. Loncastuximab is combined in a phase I trial with Durvalumab (anti-PD-L1 antibody). Blinatumomab is a bispecific T-cell engager (BiTE) which brings CD3+ T-cells in proximity to CD19+ B-cells. It is already approved for B-ALL but it has also significant activity against DLBCL[28] with a toxicity profile resembling anti-CD19 CAR-T cells. We have salvaged refractory patients with this compound and moved them to allo-HCT. Another similar molecule mosunetuzumab[29] brings CD3+ T cells close to CD20+ lymphoma cells and has single agent activity and is tested in combination with polatuzumab in a phase Ib/II trial. Mosunetuzumab is also scheduled to be combined with CHOP or with polatuzumab-cyclophosphamide-doxorubicin-prednisone. Such combination if safe is expected to be very effective. Inotuzumab ozogamicin does not seem to work well for DLBCL.[30]

It is important to emphasize that the use of BiTEs and ADCs has not been formally tested as a bridge chemotherapy before auto-HCT and the outcome of auto-HCT after responses attained with such therapies cannot be guaranteed that is equal after responses with salvage cytotoxic chemotherapy

Attempts to improve AUTO-HCT

In terms of optimization of the auto-HCT results, most attempts are focusing in the post-transplant setting. For GC-DLBCL we participate in a study of idelalisib vs placebo as a maintenance while in the ABC-DLBCL the respective trial is ibrutinib versus placebo in attempt to decrease or delay relapses. In terms of conditioning regimen the most noticeable effort was the combination of epigenetic agents (5-azacitidine and vorinostat) with the novel regimen of infusional gemcitabine-busulfan and melphalan.[31] In this regimen, gemcitabine was added to busulfan and melphalan to inhibit DNA repair. Next, vorinostat was added because histone modification was thought would increase the access of the cytotoxics to the DNA. Finally, azacytidine was added to the combination to inhibit DNA methyltransferase that was found to be upregulated previously. Azacitidine addition increased cytotoxicity in vitro. This very intense regimen was tried in both HL and aggressive NHL including 26 patients with DLBCL. Ten of 26 patients were DHL or DEL. All of them either had either primary refractory disease or less than PR in the 1st salvage or relapse <1year after R-CHOP or had received >chemotherapy lines or had high secondary IPI. One third of patients had a positive PET before transplant. At a median of 15 months of follow up, DLBCL patients had a DFS of 65% and OS of 77%. Although the number of patients is small this regimen preliminarily compares favorably to R-BEAM. It requires expertise and access to fast turnaround of busulfan levels. Another regimen that has been more promising that R-BEAM is the combination of thiotepa-busulfan-cyclophosphamide and rituximab in primary CNS lymphomas (PCNSL) that is used broadly even as consolidation to reduce relapse rates.[32,33] It can have considerable neurotoxicity especially in older patients (>75y/o) with prior cranial irradiation and requires palifermin support. It has a high enough rate of hepatic sinusoidal obstruction syndrome. In our institution, we use it in PCNSL for patients not irradiated before and with excellent performance status. Otherwise, for PCNSL, we use the combination of thiotepa with carmsutine and rituximab[34] which is less toxic.

The role of chimeric antigen receptor t cell cellular immunotherapy (CAR-T)

In the last year, the FDA has approved 2 anti-CD19 CAR-Ts for aggressive DLBCL (including TFLs and high grade B-cell lymphomas). The first one approved is the KiTE product Axicabtagene ciloleucel (Yescarta) which uses CD28 as a costimulatory molecule. This treatment has given dramatic and often durable responses in bulky and refractory aggressive B-NHL (DLBCL, TFL, HGBLs and PMBCL). The ORR was 83% and the CR rate was 58%.[35] After a median, f/u of 27 months, little more than 50% of patients are still alive and the PFS is 37%. Only one relapse happened after the first 6 months of f/u. That means that 2/3 of patients who achieve CR keep it for 6 months and after that interval the vast majority of them do not relapse again.[36] Studies in mantle cell lymphoma, follicular lymphoma and B-ALL are running using the same product with early promising results.

The other product is tisagenlecleucel by Novartis, which initially was approved for childhood and young adult B-ALL and then it was approved also for relapsed or refractory DLBCL.[37] The costimulatory molecule is 4-1BB. The ORR was 52% and the CR was 40%. Two thirds of the responders enjoyed a PFS at one year (33% of all enrolled). The costimulatory molecule 41BB is associated with longer persistence of the CAR-Ts but this translates to a higher incidence of persistent hypogammaglobulinemia and need to give monthly intravenous immunoglobulin. The initial responses (and complications) may be faster with Yescarta due to the CD28 costimulation however patients with Kymriah have been treated in the outpatient setting potentially due to lower incidence of dramatic side effects. A third product Lisocabtagene maraleucel (Liso-cel, Celgene/Juno) contain 4-1BB and a fixed CD4:CD8 ratio and in 37 patients with advanced DLBCL the ORR was 78% and the CR was 62% with most patients of these patients stay in remission at 6 months.[38] This product seems to have the best toxicity profile from all 3 but it is not yet FDA-approved. Since a PD-1 upregulation has been observed in CAR-T cells few days after infusion, investigators combine anti-PD(L)1 inhibitors to CAR-T cells in an effort to prolong their effect. Although re-expansion is achieved it is unknown if this translates to better efficacy. Similarly companies try to combine anti-CD20 antibodies with anti-CD19 CAR-T cells and lately immunostimulatory molecules like lenalidomide. The results of such efforts remain to be seen and the mechanisms of resistance other than CD19 negative cell escape (and potentially PD1 upregulation) need to be elucidated. Gene transfer through replication-deficient viruses into the T-cells and expansion require about 3 weeks from the time of leukapheresis and patients are first treated with lymphodepleting chemotherapy (typically fludarabine-cyclophosphamide) to achieve in vivo expansion of CAR-T cells through lymphopenia-induced proliferation.

The treatment is toxic and patients develop cytokine release syndrome with hypotension, hypoxia, third spacing and potentially acute kidney injury and this is treated with vasopressors, tocilizumab and in severe case corticosteroids. The other major severe toxicity is neurotoxicity which is dramatic in

presentation with consciousness alteration and aphasia, apraxia, ataxia, dysgraphia, dyscalculia and orientation/memory problems as well as seizures. This is treated with steroids. The most severe form of neurotoxicity is cerebral edema albeit rare is lethal.[39] The treatment-related mortality of the procedure is about 3% in experienced hand. Earlier administration of tocilizumab and steroids have decreased toxicity in my experience but it is unknown the effect of these manipulations especially steroids in the duration of the therapeutic efficacy.[40,41] Preventive treatment with tocilizumab was not effective and neurologic toxicity including cerebral edema could not be avoided. In practice the most serious toxicity is probably the financial one (cost to insurance is ~$800,000) which leads to a multi-factorial delay in the treatment approval and frequently to the patient demise. One critical question is if patients who attain CR with CARTs should be moved to allo-HCT if and available donor is available. This maybe the only window that some of these patients have to go to transplant. In our hands allo-HCT does not work if the disease relapses after CAR-T therapy even if the disease goes back to CR with either a second CAR-T infusion or with irradiation of residual masses. Since 2/3 of patients who attain CR will stay in remission and it is not predictable who will be the 1/3 of patients who will relapse we believe that only a clinical trial will answer reliably this difficult question.

Recently, anti-CD22 CARTs have shown efficacy in patients with B-ALL and CD19 negative escape. A very promising strategy is the inclusion of 2 separate chimeric antigen receptors to the same T-cell one with activity against CD19 and the other with anti-CD22 activity each one with different costimulatory molecules (OX40 and 4-1BB). Such cells (bicistronic CAR-T) are constructed by Autolus Ltd in United Kingdom and have already shown preliminary safety and activity either alone or in combination with pemprolizumab early in the treatment course.

CAR-T cells are still early in their early development[42] and future combinations with other active molecules like polatuzumab or CD19 ADC or CD19/CD20 BiTE are needed but the cost of the treatment will go higher and the companies are afraid of extra-toxicity which may harm their products. The full array of CAR-T toxicities and their mechanisms need to be studied more. Hemophagocytic lymphohistiocytosis/macrophage activated syndrome has been reported as well as ongoing bone marrow dysfunction with long-term cytopenias and even MDS with characteristic cytogenetic abnormalities; however, it is possible that previous treatments play a significant role in the development of the latter (Navas G, Lekakis L et al, accepted at TCT 2019 meetings). The real-world experience with Yescarta has been recently presented and it does not seem to differ from the original trial (Nastoupil et al, ASH 2018).

Suggested guidelines for treatment of relapsed/refractory DLBCL in the transplant-eligible population

There are 2 main questions:

1) Are there cases that the standard approach of salvage chemotherapy followed by auto-HCT should not even be started due to expected futility?
2) What kind of PET response to salvage in certain biologic subtypes is considered suboptimal to abort the salvage/auto-HCT attempt and to change treatment modality?

It is noteworthy that contemporary trials try to answer formally such questions. For example, the ZUMA-7 trial randomizes patients with primary refractory or relapsed within a year after RCHOP patients to either salvage/auto-HCT or Yescarta alone. The study still accrues and results are not available yet.

In Figures 1 to 4, we have summarized our suggested approach. This represents only authors' suggestions and they are not official guidelines of any organization.

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