Chapter 13

Post-Heart Transplantation Lymphoproliferations

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Additional information is available at the end of the chapter

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Abstract

Post-transplant lymphoproliferations (PTLDs) are the cancer with the highest incidence after cardiac transplantation. The World Health Organization (WHO) has defined several specific entities: clonal or non-clonal, early, polymorphic or monomorphic. Early PTLDs being generally positive for Epstein-Barr virus (EBV), preventive and preemptive treatments have been proposed; the former did not lead to effective attitudes, unlike preemptive treatment, based on EBV viral load monitoring the first year, which proposes a decrease of the immunosuppression with or without rituximab according to the viral load and the answer to the immunosuppression decrease. The curative treatment of CD20 positive PTLDs, the most frequent form, begins to be codified; it starts with a decrease in immunosuppression and then uses rituximab monotherapy and, depending on the response, either only rituximab or four courses of R-CHOP. By following this management, the incidence of early PTLDs decreases and the treatment of PTLDs provides survivals close to that of other transplant patients.

Keywords: post-transplant lymphoproliferation, epstein barr virus, lymphoma, rituximab

1. Introduction

Non-Hodgkin's lymphoma (NHL) is the cancer with the highest incidence after cardiac transplantation. However, NHL is only part of the PTLD, the WHO recognizing several entities, whose lymphomatous and/or clonal appearance is not systematic. Since PTLDs are often linked to Epstein-Barr virus (EBV), preventive and above all preemptive treatments have been proposed to reduce the incidence of these proliferations. The prognosis of PTLD is generally presented as severe; however, the latest therapeutic proposals, adapted to the response to rituximab, provide survivals close to those of the rest of the population of transplanted patients.

2. Epidemiology

It is usual in the literature to estimate between 3 and 5% the risk of a cardiac-transplanted patient developing a PTLD [1]; however, these figures are old and vary depending on immunosuppression and duration of patients' lives, fortunately improved in the last 10 years. The largest study on the epidemiology of PTLD [2] involved 175,732 organ transplants between 1987 and 2008, including 10% of heart transplants. Pulmonary cancers represent the most frequent cancers (386/100,000/years) just in front of the NHL (283/100,000/years) but the standardized incidence ratio (SIR) of the NHL is very clearly superior to that of all the other cancers. **Table 1** presents the incidence and the SIR of the main cancers according to the transplanted organ. The risk of PTLD persists as long as immunosuppression is used, that is, until death for cardiac transplant patients; it is maximum the first year after transplantation, with an SIR greater than 10, but remains stable thereafter, with a SIR between 3 and 10 for a follow-up of up to 15 years.

Transplanted organ	Cancer: incidence (100,000/years)/SIR			
	NHL	Lung cancer	Liver cancer	Kidney cancer
Heart	283/7.79	386/2.67	13.8/1.02	90.1/2.90
Kidney	141/6.05	115/1.46	10.7/1.08	126/6.66
Liver	217/7.77	178/1.95	495/44	39.9/1.80
Lung	532/18.73	626/6.13	17/2.04	34/1.49

Table 1. Incidence and SIR of the main cancers developed after transplantation depending on the transplanted organ.

EBV, initially described as always associated with PTLDs, is actually only half of the time. Almost always found in children, most often on the occasion of a primary infection, and in early forms (before the first year after transplantation), it has become rare in the late forms, the most common situation of our days [3]. In cerebral PTLDs, representing 10% of PTLDs, EBV is almost always found [4].

3. Diagnosis

3.1. Definition: anatomopathology

PTLDs, as their name suggests, are lymphoid proliferations occurring after solid or hematopoietic organ transplantation and are authentic entities recognized in the WHO classification [5], presented in **Table 2**. We will retain some peculiarities to this classification:

- Early lesions are almost always EBV positive.
- Polymorphic lesions (infiltration by cells of different types) are polyclonal in almost half of the cases.
- Monomorphic lesions are clonal.

- The cerebral PTLDs are almost always monomorphic B lesions.
- B-type diffuse B-cell monomorphic lesions are by far the most common PTLD.
- Follicular lymphomas, marginal zone lymphomas, and mantle cell lymphomas are not considered PTLDs even when they occur after transplantation.

Early lesions	**Plasmacytic hyperplasia PTLD**
	Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD	
Polymorphic PTLD	
Monomorphic B PTLD	Diffuse large B cell lymphoma
	Burkitt lymphoma
	Plasmacytoma-like
Monomorphic T PTLD	T-cell lymphoma, non-otherwise specified
	Hepatosplenic T-cell lymphoma
	T/NK lymphoma
Classical Hodgkin lymphoma PTLD	

Table 2. WHO classification for PTLD.

3.2. Diagnosis and extension assessment

The presentation of PTLDs is not unambiguous and the signs are not specific. In early forms, an alteration of the general status with fever is often present. In the other forms, the clinical signs depend on the tumoral localizations; for this reason, the digestive localizations are frequent and can be a source of digestive disorders, pain, even perforation, or necrosis (**Figure 1**).

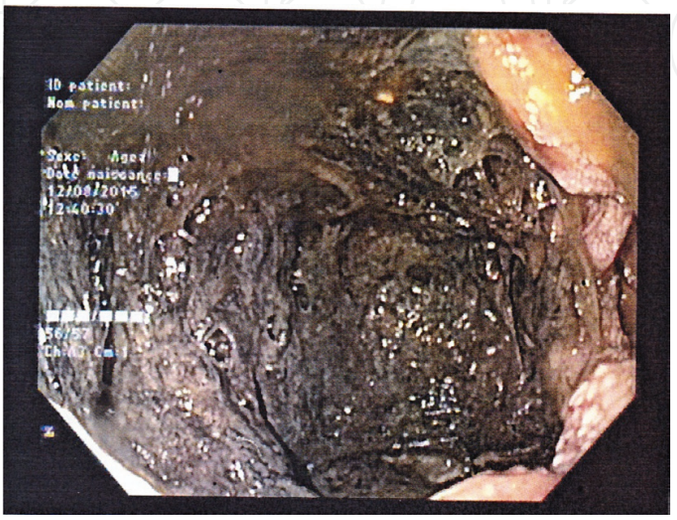

Figure 1. Gut necrosis due to a PTLD.

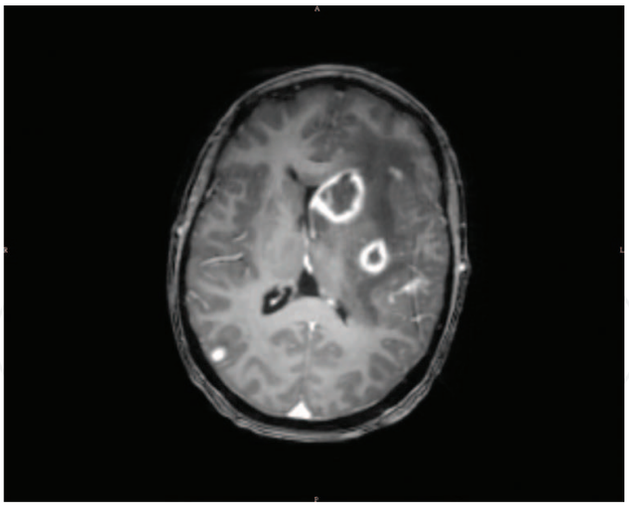

Figure 2. Cerebral PTLD, MRI in T1 with gadolinium.

Paraclinically, the EBV viral load (EVL) is essential, and a high rate is in favor of an EBV-positive PTLD; it is also a good marker of response during treatment. Imaging, CT scanning, or especially PET-CT scan are diagnostic [6] and allow an adequate extension assessment. The appearance of tumors and nodes is similar to that of lymphomas of immunocompetent patients. In the particular case of cerebral PTLD, the lesions are necrotic, in the form of a cockade, identical to toxoplasmic lesions, as in patients with HIV (**Figure 2**). MRI spectrometry can point to PTLD rather than infection. In the absence of contraindication, a lumbar puncture is necessary; it must include a cytology with anti-CD20 labeling on a slide, a phenotyping, a search for B clonality, and an EBV viral load. If lumbar puncture is found in lymphoma cells, cerebral biopsy is not necessary.

4. Treatment

4.1. Preventive treatment

Preventive treatment is defined as a systematic treatment that can avoid or reduce the incidence of PTLDs; it only concerns EBV-positive PTLDs. In this area, no study specifically targets heart-transplant patients. The interest of antivirals, especially ganciclovir, does not seem to be confirmed. On the other hand, polyvalent CMV immunoglobulins (in fact rich in anti-EBV immunoglobulins) have shown, in a retrospective study, an interest in kidney-transplant patients, suppressing the risk of PTLD occurring during the year of prevention in more than 2000 patients [7], whereas no preventive effect was detected in patients receiving ganciclovir. However, a prospective study, admittedly of a smaller size, did not show any difference between a preventive treatment with ganciclovir + placebo versus ganciclovir + immunoglobulins against CMV [8]. Currently, no preventive treatment is recommended in cardiac-transplant patients.

4.2. Preemptive treatment

Preemptive treatment only concerns EBV-positive PTLDs; it consists of treating patients according to their EBV viral load. It is based on the fact that the majority of EBV-positive

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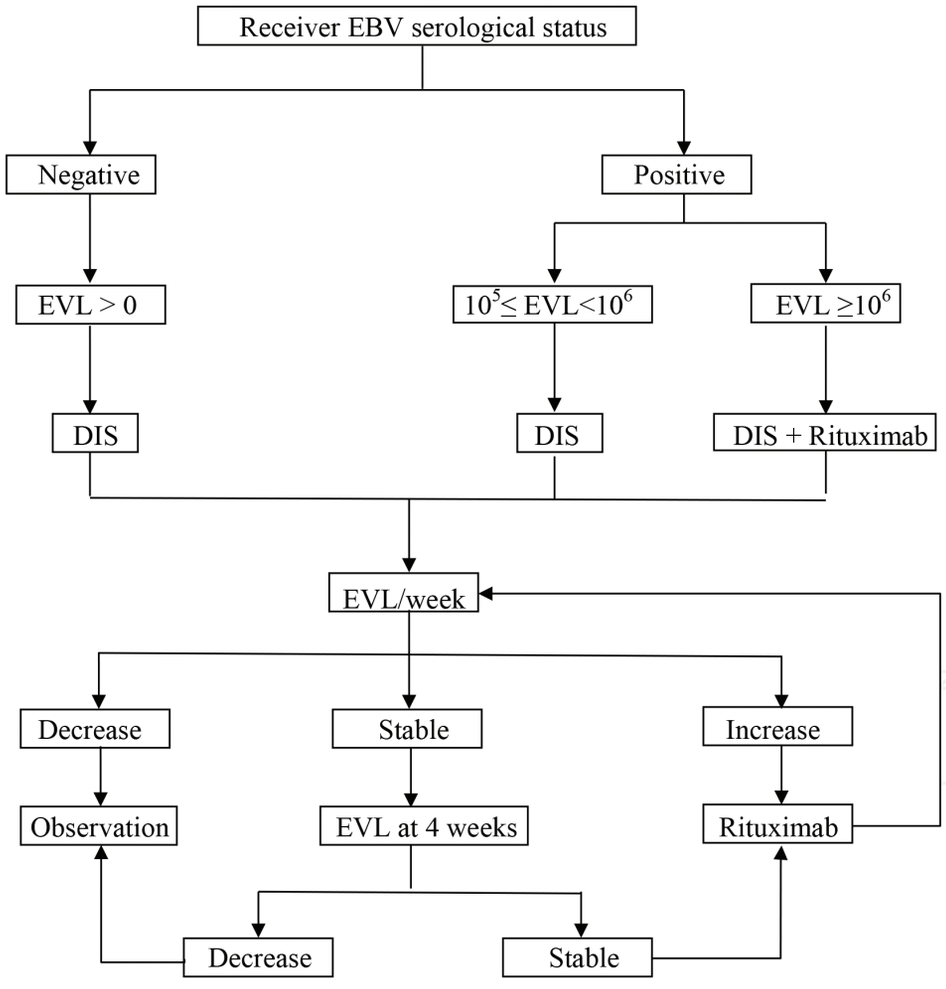
PTLDs are preceded by an increase in EBV load or a simple positivity in the case of primary infections [8]. The most classic attitude is to reduce immunosuppression, where possible [9–11]. As the EBV reservoir is the B lymphocyte, rituximab has also been used successfully in this setting, especially after allografts of hematopoietic stem cells [12]. Much less available and usable only in the context of protocols, anti EBV T lymphocytes, either autologous (taken from the patient and stimulated ex vivo) [13, 14], or allogeneic (from healthy donor lymphocyte banks) [15], have been used effectively in case of EBV reactivation. Specifically developed in cardiac-transplant patients, a treatment algorithm has been validated on nearly 300 patients whose immunosuppression was identical [16]; it is based initially on the serological status before transplant and then on the EVL carried out at each follow-up visit, for at least 1 year. The algorithm is described in **Figure 3**. In summary, immunosuppression is reduced as soon as the EVL is positive if the recipient was seronegative, since it is then a primary EBV infection, that is, when the EVL is greater than 10^5 copies/ml in other case.



EVL = EBV viral load (copies/ml)
DIS = decrease of immunosuppression
Rituximab = one injection of 375 mg/m² IV

Figure 3. Algorithm for preemptive treatment of PTLD after heart transplantation, depending on serological status and EBV viral load.

An injection of 375 mg/m^2 of rituximab is performed, in addition to the decrease in immunosuppression, if the EVL is greater than 10^6 copies/ml, or if the initial decrease in immunosuppression fails. No cases of EBV-positive PTLD were diagnosed in this series, which is statistically significant in historical comparison with more than 800 patients transplanted in the same unit before using this algorithm.

4.3. PTLD treatment

4.3.1. Decrease of the immunosuppression

The decrease in immunosuppression remains the benchmark for the initial management of PTLDs. It allows complete response in less than 10% of cases, mainly in early forms [17, 18]. As the median time of response is 3.6 months [19], it is conventional to wait 4 weeks before evaluating the response to the decrease of immunosuppression, except in case of progression. Even in the event of failure, it is necessary to keep the immunosuppression as low as possible because it seems to potentiate immunochemotherapy [20].

4.3.2. Immunochemotherapy

In the case of failure of the reduction of immunosuppression, in CD20-positive PTLDs, which represents the vast majority of cases, sequential immunochemotherapy is the reference treatment, validated by two European prospective studies [3, 21]. The processing algorithm is shown in **Figure 4**. The first phase is to use only rituximab monotherapy and wait 3 weeks before evaluating the response, in case of complete remission, which is found in one-third of cases; rituximab is continued alone, this to avoid chemotherapy, in other cases, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) is used, a reference chemotherapy of NHL, but only for four cures against six to eight in the immunocompetent patients, and a case is presented in **Figure 5**. This therapeutic attitude gives 88% of response, 70% of complete response, and a median survival of 6.6 years, which currently constitutes the best results of the literature for a prospective study. In pediatric patients, lightened chemotherapy regimens have been proposed, without doxorubicin or vincristine, making it possible to obtain an overall survival of 83% at 2 years and an event-free survival of 71% [22].

4.4. Specific PTLDs

4.4.1. PTLD of the central nervous system

PTLDs in the central nervous system account for 10% of PTLDs, and even if they occur mostly after kidney transplants, they are not uncommon after cardiac transplantation. Their management is not consensual but should include if possible a reduction of immunosuppression and methotrexate adapted to the renal function, and the addition of aracytine and rituximab is recommended. In case of failure or contraindication, radiotherapy is an option. In a recent retrospective study, the response rate was 60% but the 3-year survival was only 43% [4].

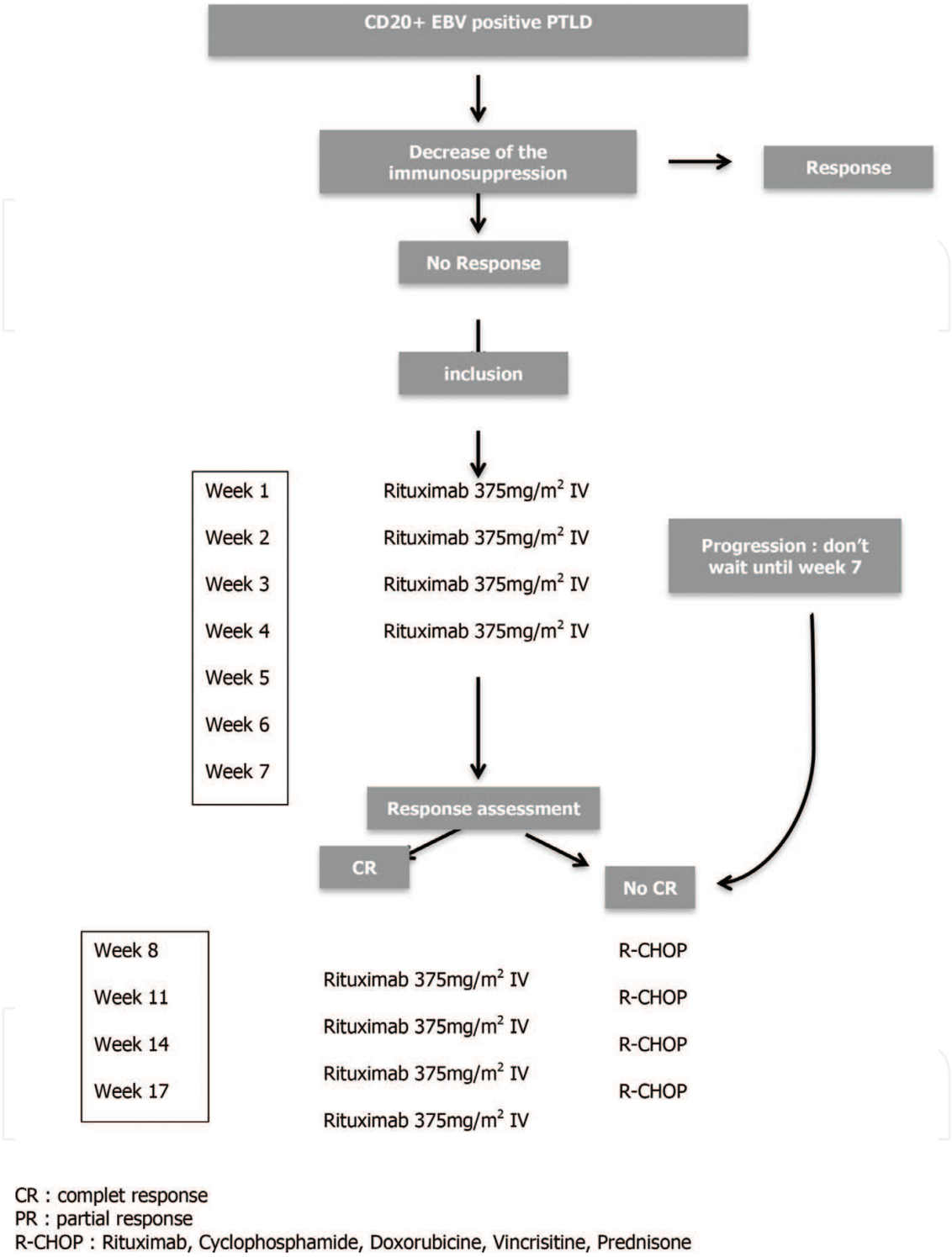


Figure 4. Algorithm to treat CD20-positive PTLD in first line.

4.4.2. Classical Hodgkin PTLD

Hodgkin PTLD should be treated as Hodgkin's immunocompetent patients, without rituximab (Hodgkin's are CD20 negative); their prognosis is excellent.

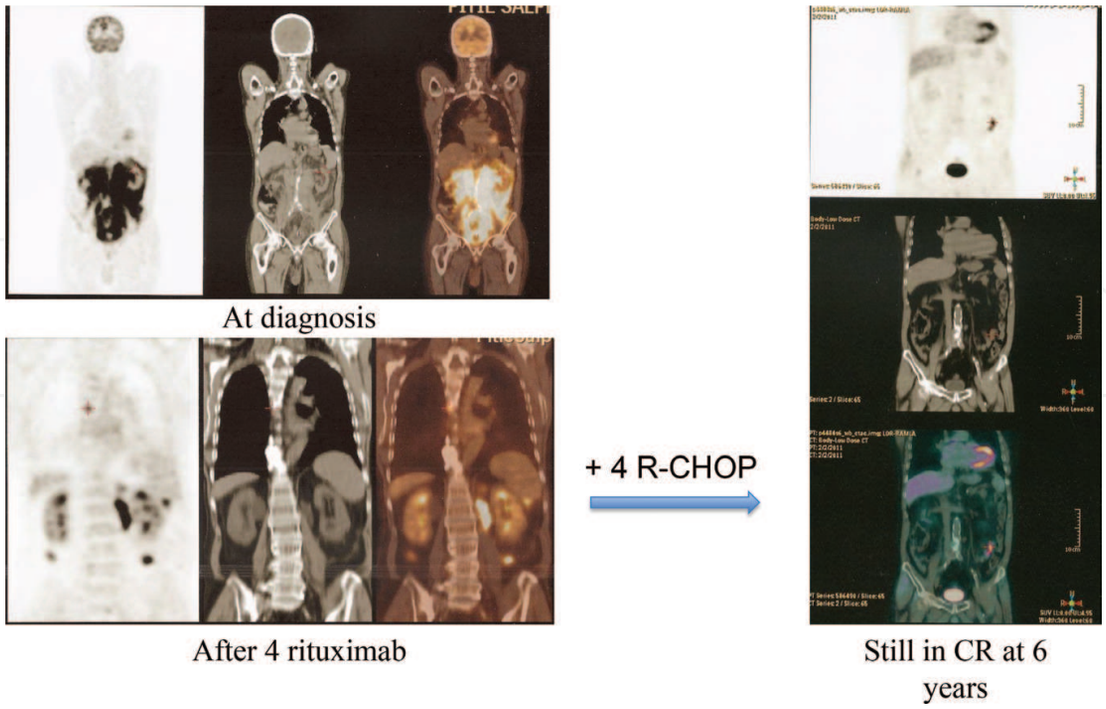


Figure 5. Response of a monomorphic diffuse large B cell PTLD after four rituximab and after four R-CHOP.

4.4.3. Plasmacytic hyperplasia PTLD

This rare form of early lesions can be treated with radiotherapy or lymphoma chemotherapy.

4.4.4. T-cell lymphoma PTLD

This type of PTLD has a very poor prognosis, rituximab is useless and the classic chemotherapy-type CHOP has little effectiveness. In case of localized form, radiotherapy may be useful.

4.4.5. Relapses

Relapses after complete remission are rare; if they occur late after the first PTLD, a comparison of the clones is necessary because a second PTLD, independent of the first one, is possible; if it is the case, the algorithm of first line, describes previously, can be reused, and the maximum dose of anthracycline will not be reached. In other cases, NHL treatments of immunocompetent patients in relapse may be used, even hematopoietic stem cell autograft.

4.5. Cell therapy

Cell therapy is not yet available outside study protocols. Its principle is to use T cells specifically directed against EBV antigens, so it is only applicable to half of PTLDs. It is mostly the allogeneic lymphocyte banks, from healthy donors, that are promising. The lymphocytes are selected according to the HLA typing of the tumor. In the Scottish experience, 12

complete remissions were obtained from 33 treated patients, but many of these patients had not received rituximab in the first line [23]. The ATARA Biotherapeutics laboratory begins in 2018, a phase 3 study using allogeneic anti-EBV lymphocytes against placebo in relapsed or refractory PTLDs, which could allow in the medium term to offer this therapy to all centers treating PTLDs.

4.6. CAR-T cells and anti-PD1/anti-PDL1

CAR-T cells, which are being developed in lymphoid hemopathies of immunocompetent patients, have not yet been used in an immunocompromised context that could potentially reduce their effectiveness.

Anti-PD1/PDL1 antibodies by improving immunity expose patients to rejection of the transplanted organ, sometimes abruptly; their indication in PTLDs, mainly of Hodgkin type, is strongly discouraged and should only be proposed by the last resort [24].

5. Conclusion

PTLDs are a clearly defined entity, representing the most increased cancer among cardiac-transplant recipients compared to the general population. Its management, from preemptive treatment to curative treatment, has been considerably improved in order to obtain a survival rate similar to that of other transplant recipients. The treatment deviates significantly from that of immunocompetent lymphomas and requires management by teams accustomed to this type of pathology, both for the follow-up of the transplant and for the hematological treatment. The development of cell therapies is very likely the next step in progress.

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