TEZĂ DE DOCTORAT – Rezumat

Imunoterapie post autografa in tratamentul limfoamelor

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CUPRINS

CONTRIBUŢIA PERSONALĂ

Cuvinte cheie: Limfom malign, terapie celulara autologa, imunoterapie, Rituximab, Interferon

Introducere

Limfoamele non-Hodgkiniene reprezinta patologie maligna manifestata printr-o proliferare clonala a tesutului limfoid. Aceasta proliferare clonala a limfocitelor este caracterizata printr-o mare variabilitate de prezentari clinice, tipuri histologice si etiologii ceea ce face ca evolutia, tratamentul si prognosticul limfoamelor sa fie extrem de diferite.

In ultimii ani au realizate progrese importante in diagnosticul si tratamentul acestui tip de hemopatii permitand transformarea imaginii limfoamelor din boli mortale in boli potential curabile. In mod clasic tratamentul modern al limfoamelor asociaza utilizarea anticorpilor monoclonali si cea a chimioterapiei conventinale. In ciuda excelentelor rezultate obtinute prin diferitele tehnici de tratament, exista inca un numar important de resute. Acest lucru se datoreaza fie selectiei unor clone de celule rezistente la chimioterpia intensiva sau a existentei unor celule suse tumorale, care nu pot fi expuse la chimioterapia conventionala. Pentru eliminarea acestor celule – maladie reziduala indetectabila – este necesara dezvoltarea de noi tehnici de tratament.
Recent, s-a dezvoltat o noua tendinta in tratamentul limfoamelor: imunoterapia ce vizeaza eliminarea maladiei reziduale indetectabile cu cat mai putine efecte secundare; ea poate imbraca o forma activa sau pasiva. In 1997 Slavin S si Nagler A, de la Univeristatea din Tel Aviv, publica rezultatele unui studiu efectuat in care arata in cazul bolnavilor cu limfom care au beneficiat de o intensificare terapeutica (autogrefa), imunoterapia pasiva, prin interferon alfa si interleukina 2, permite ameliorarea rezultatelor obtinute prin procedura de autogrefa, permitand in acest fel confirmarea faptului ca imunoterapia pasiva poate elimina maladia reziduala indetectabila. In cazul lucrarii de fata am utilizat in tratamentul bolnavilor purtatori de limfom o tehnica de imunoterapie pasiva care asociaza utilizarea anticorpilor monoclonali de tip Rituximab (Mabthera), interferon alfa si interleukina 2.

Aspecte moderne in tratamentul limfoamelor

Terapia celulara autologa reprezinta un tratament extrem de important pentru pacientii diagnosticati cu limfom agresiv cu celule mari, in special pentru pacientii cu factori de prognostic infaust in momentul diagnosticului (IPI>/=2) sau pentru pacientii refractari sau in resuta dupa o prima linie de tratament ce include o chimiotherapie pe baza de antracicline . Acesta prima lucrare, devenita referinta in tratamentul limfoamelor agresive in resuta, arata o crestere a ratei de supravietuire fara maladie de 46% la cinci ani pentru pacientii autogrefati, fata de 12% pentru pacientii care nu au beneficiat de autogrefa. In epoca rituximabului rezultatele sunt ameliorate datorita activitatii sinergistice chimioterapie+imunoterapie, dar exista inca diferente majore intre pacientii transplantati si cei care nu pot beneficia de autogrefa Daca lucrurile au fost clarificate pentru limfoamele hodgkiniene sau pentru limfoamele cu celule mari, in cazul celorlate tipuri de limfoame mai exista inca controverse, care par sa se accentueze cu aparitia terapiilor tintite (anticorpilor monoclonali sau a terapiei moleculare).

Tratementul clasic, prin chimioterapie sau radioterapie a evoluat intr-o maniera spectaculara in ultimii 50 de ani. Cateva date au marcat profund tratamentul acestui tip de tumori: aparitia in anii 60 a antraciclinelor, aparitia in anii 70 a conceptului de autotransplant, aparitia factorilor de crestere, aparitia in anii 90 a terapiei tintite si in special a Rituximabului. Toate aceste schimbari au facut ca o mare majoritate a limfoamelor sa se schimbe ca prognostic, trecand de la conceptia de boli letale la boli potential curabile.
Exista insa inca o mare varietate de limofame pentru care tratamentul actual nu permite eradicarea tumorii ci numai obtinerea unor remisiuni de mai lunga sau mai scurta durata.
Alaturi de cresterea cantitatii de informatii care permit o mai buna intelegere a mecanismelor intime ale limfogenezei este necesara dezvoltarea unor noi terapii care sa permita o mai buna tintire a celulelor tumorale avand in acest fel mai putine efecte indezirabile.
In ultimii ani este o noua tendinta in tratamentul limfoamelor: imunoterapia. Aceasta poate imbraca o forma activa sau o forma pasiva, scopul fiind acelasi, eliminarea maladiei reziduale cu cat mai putine efecte secundare. Intelegerea mecanismelor intime de actiune a anticorpilor monoclonali permite o abordare logica a posibilitatilor de ameliorare a acestora. Mecanismele prin care anticorpii monoclonali pot distruge celula tinta cuprind intre altele: citotoxicitate celulara mediata de anticorpi (ADCC), toxicitatea directa, citotoxicitate celulara mediata de complement (CDC),un posibil efect vaccinal.

Ipoteza de lucru

Studiul nostru se inspira din rezultatele obtinute de Nagler et al. In cadrul unei imunoterapii postautotransplant am asociat, conform studiului precedent, interferon alfa si interleukina 2, la care am adaugat un anticorp anti CD20 – Rituximab. Efectul antitumoral al rituximabului in cadrul tratamentului lifoamelor de tip B a fost deja demonstrat in foarte multe studii. Mecanismul de actiune al acetui anticorp este multifactorial: modularea

influxului/efluxului calcic la nivel celular, toxicitate celulara dependenta de complement – CDC, toxicitate celulara dependenta de anticorpi ADCC.

Am luat incosiderare in studiul de fata pacienti tratati pentru limfom, pacienti carora le-am administrat o imunoterapie in situatia de maladie reziduala indetectabila, post autografa. Aceasta imunoterapie a constat in administrarea, in momentul iesiri din aplazie, a 4 perfuzii saptamanale de Rituximab, urmate de administrarea a 2 blocuri de cate 7 saptamani de rINF alfa si IL2. Am comparat rezulatele obtinute cu o cohorta standard, care nu a beneficiat de aceste tratamente. Au fost evaluate intre cele doua cohorte, in totalitate si apoi in cadrul subgrupurilor de pacienti, supravietuirea fara boala si supravietuirea globala. Perioada aleasa a fost necesara pentru a avea un real tablou al rezultatelor obtinute.

Pacienti si metoda

In perioada 2000 – 2003 am identificat 64 pacienti cu limfom, care au beneficiat de terapie celulara autologa in Centrul de Transplant Brest, Franta.
Diagnosticul de limfom a fost pus dupa examenul anatomopatolgic al unei piese de biopsie. Pentru diagnostic s-au folosit examene citologice, citogenetice, imunofenotipice si de biologie moleculara conform reglementarilor revazute OMS 2005.
Bilantul de extindere al limfoamelor s-a facut prin examen tomodensitometric toraco-abdomino-pelvian, biopsie osteomedulara si punctie lombara diagostica. Stadializarea s-a facut in functie de scara ANN-ARBOR. Pentru bolnavii in caua s-au calculat indici prognostici IPI si FLIPI, dar nu s-au facut analize statistice comparative in functie de acesti parametri.
Diagnosticul final a fost exprimat dupa recomandarile OMS 2005
Pacientii au beneficat de chimioterapie adaptata fiecarui tip de limfom, dupa recomandarile Societatii Franceze de Hematologie. Evaluarea raspunsului s-a facut in functie de bilantul initial. Raspunsurile au fosta standardizate dupa protocolul de raspuns descris de Cheason in 1999.
Pacientii au fost spitalizati in sectorul protejat al Centrului de Transplantare de Maduva Osoasa Brest, Franta. Dupa verificarea normalitatii bilantului heapatic si renal este inceputa chimioterapia de conditionare a grefei. Pe toata perioada de spitalizare pacientii au beneficiat de o hidratare continua cu glucoza 5%. In perioada de conditionare s-a efectuat o hiperhidratare cu glucoza 5% la care s-a adaugat bicarbonate\ 1,4% pe o cale venoasa centrala. Preventia antiemetizanta a fost efectuata printr-o dubla administrare dd\e Zophren si Plitican. Conditionarea autotransplantului s-a efectuat exclusiv prin chimioterapie. Protocoalele de chimioterapie utilizate au fost:
BEAM - BCNU 300 mg / m2 J-6
VP16 200 mg / m2 J-5 J-4 J-3 J-2
ARA-C 200 mg / m2 J-5 J-4 J-3 J-2
MELPHALAN 140 mg / m2 J-1
Sau
CBV-Novontrone.
Pacienti au beneficiat in continuare de imunoterapie pasiva care a constat la inceput prin administrarea de patru perfuzii saptamanale de rituximab (Mabthera®, Roche) la doza de 375mg/m², urmata in continuare de administrata in doua blocuri de cate 7 saptamani de interferon, si interleukina 2.
Pacientii au primit
Interferon alfa, 1.5 milioane de unitati, in injectii subcutanate, odata pe zi
Interleukina 2 (Proleukin®), 6 milioade de unitati o data pe zi.
Nu exista diferente statistic semnificative intre cohorta de pacienti care au beneficiat de imunoterapie postautografa si cohorta de pacienti care nu a beneficiat de aceasta terapie post autografa.

Rezultate

Analiza datelor la 5 ani arata:
- o supravietuire fara maladie de 75% pentru bonavii care au beneficiat de imunoterapie fata de 44% in cazul bonlnavilor care nu au beneficiat de consolidare
- o supravietuire globala de 81% pentru pacientii care apartin primei cohorte fata de 56% pentru pacientii apartinand celei de-a doua cohorte (pacienti fara imunterapie).

Rezultatele obtinute in cadrul analizei studiului de fata confirma datele obtinute de Nagler in 1997; ele sunt in conforrmitate cu celelalte date publicate in literatura. Administrarea unei imunoterapii post grefa in cazul pacientilor tratati pentru un limfom, indiferent de tipul de limfom, permite ameliorarea supravietuirii globale si a supravietuirii fara maladie. Acest lucru este mai evident in momentul analizei rezultatelor obtinute la 5 ani. In cazul resutelor, acestea apar de o maniera precoce, proba timpului reperezantand un important factor predictiv.

In urma acestor rezultate am analizat efectul imunoterapiei asupra principalelor tipuri de limfom care exprima la suprafata celulelor antigenul CD20: limfomul folicular, limfomul difuz cu celule mari si limfomul de manta.
Din pacate numarul de pacienti pe tip de subgrup (cu exceptia limfomului difuz cu celule mari) este destul de restrans. In aceasta situatie este dificil de efectuat evaluari statistice analitice. Ne vom rezuma deci numai la analiza descriptiva a fiecarui subgup

Discutii

Rezultatele publicate pana in acest moment asupra efectelor antitumorale ale celor doua molecule, interferonul alfa si interleukina 2, lasa sa se intrevada un efect sinergic al asocierii celor doua molecule. Dupa procedura de autografa, nivelul seric de interleukina 2 ramane foarte scazut pe o durata ce poate atinge 18 luni. Aceasta scadere importanta a unei citokine cu implicatii majore in activarea si stimularea proliferarii elementelor imunitatii celulare ridica o serie de probleme importante privind reconstitutituirea imunitatii naturale antitumorale si asupra eficacitatii acestui proces natural de aparare a organismului. Reinjectarea unor contitati terapeutice de interleukina 2 post grefa permite obtinerea unor niveluri serice apropiate de normal a acestui activator natural al imunitatii celulare, permitand in acest fel o restaurare, cel putin partiala, a efectului antitumoral si a supravegherii imunologice. Se preconizeaza in acest fel obtinerea unei diminuari a riscului de recidiva pecoce, de alftel cunoscut ca principal mecanism de reactivare a celulelor suse tumorale limfoide. Mecanismul prin care IL 2 realizeaza acest obiectiv terapeutic este o stimulare a recuperarii limfocitelor NK si LAK si pe termen lung, recuperarea functionala si a numarului efectorilor T CD4 si CD8 pozitivi. Asocierea celor doua molecule, interferonul alfa si interleukina doi, are ca si scop pe de-o parte cresterea prezentei la suprafata celulelor tumorale a antigenilor de histocompatibilitate de tip 1 sau de tip 2, cresterea de asemenea a prezentarii antigenice de catre celulele dendritice permitand in acest fel o mai buna recunoastere de catre efectorii imunitatii celulare activati prin IL2. Imunosupresia indusa de catre procesul de autografa poate dura pana la 18 luni, in aceasta perioada crescand susceptibilitatea la infectii bacteriene sau virale. Recostitutia imunologica este un proces gradual, de durata variabila. Recuperararea citotoxicitatii celulare mediate prin limfocite de tip CD16 CD56 (tip NK) devine perceptibila in cele doua saptamani dupa procedura de grefa. Procesul de recuperarea limfocitara NK poate fi accelerat, in vitro, prin administrarea de Intereleukina 2 si Interferon; aceasta recuperarea poate avea ca efect o crestere imporantanta a efectului antitumoral direct sau prin ADCC mediat de Rituximab.
In cadrul lucrarii de fata, putem observa o recuperare imunologica rapida prin administrarea acestui regim de imunoterapie. Rezultatele obtinute confirma rezultatele prezentate initial de Nagler et al. In 1997. Putem constata o diminuare a riscului de resuta, o crestere a duratei de supravietuire fara boala si a supravieturii globale in cazul pacientilor tratati prin imunoterapie tripla. Efectele adverse ale acestei imunoterapii sunt relativ minore, tranzitorii si reversibile. Rezultatele bine obtinute cu aceasta terapie in tratamentul limfoamelor, in acest studiu monocentric, atesta efectul favorabil al triplei imunoterapii – Rituximab, Interferon alfa si Interleukina 2, in situatia de maladie reziduala nedetectabila – dupa o terapie celulara autologa, dar efectele antitumorale trebuie verificate in cadrul unor studii randomizate.

Concluzii

Se observa din rezultate obtinute din analiza celor doua cohorte de pacienti, ca administrarea imunoterapiei triple in situatie de maladie reziduala minima post autografa, permite imbunatatirea rezultatelor obtinute prin procedura de autografa, in ceea ce priveste supravietuirea globala si supravietuirea fara boala. In plus, in cazul pacientilor, care au beneficiat de administrarea triplei imunoterapii si care au recazut, am observat ca recaderile sunt mai putin agresive. Analiza subgrupurilor de pacienti arata, in ciuda numarului mic de pacienti, ca rezultate interesante pot fi obtinute prin administrarea acestei terapii in cazul limfomului folicular, folicular transformat si al limfomului difuz cu celule mari.
Lucrarea de fata, desi numarul de pacienti din fiecare cohorta este destul de limitat, confirma rezultatele din literatura si deschide calea catre o noua tendinta de imunoterapie pasiva in tratamentul hemopatiilor maligne.

Curriculum Vitae

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PhD Thesis - abstract

Post autologous stem cell transplantation immunotherapy in the treatment of lymphoma

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Keywords : Lymphoma, autologous stem cell transplantation, immunotherapy, rituximab, interferon

Introduction

Non-Hodgkin lymphomas are malignant diseases characterized by a clonal proliferation of lymphoid tissue. This aberrant proliferation of lymphocytes results in a large variety of clinical presentations, histological types and etiologies, making the evolution, treatment and prognosis of lymphomas to be extremely variable.

During the lasts decades important progress was made in the diagnosis and treatment of lymphomas, allowing a change of paradigm: the lymphoma is not seen nowadays as a lethal, but rather as a potentially curable disease. Usually, the modern treatment of lymphoma associates monoclonal antibodies and classical chemotherapy. Despite very good results obtained by modern therapies, there still are an important number of relapses after treatment. The relapses are due to the selections of clones which developed cross resistance to classical or intensive chemotherapy, or to the hypothetical existence of "lymphoma stem cells", which cannot be exposed to the chemotherapy. To eliminate these resisting cells – the residual disease – is necessary to develop new strategies of treatment.
Recently, a new strategy emerged in the treatment of lymphoma: immunotherapy. This approach targets the minimal residual disease, with fewer side effects. Immunotherapy can be active or passive.
In 1997, Slavin S and Nagler A. from the University of Tel-Aviv, showed, in a very interesting paper, that the patients who underwent autologous stem cell transplantation for the treatment of lymphoma a treatment by post autologous transplantation immunotherapy associating interferon and interleukin 2 could improve the results obtained by transplantation alone. In this way it was proved for the first time the existence of minimal residual disease that can be eliminated by immunotherapy.
In the work presented here, we used passive immunotherapy for the patients who underwent autologous stem cell transplantation for lymphoma. This treatment associates monoclonal antibodies – rituximab- to interferon alfa and interleukin2.

The modern treatment of lymphoma

Autologous stem cell transplantation represents a very important treatment strategy for the patients with diffuse large B cell lymphoma, especially for those with bad prognostic factors or for those with refractory or relapsed disease. The first published data that became a reference in the field, found an increased five years progression survival for patients which underwent autologous stem cell transplantation (46%) compared to patients not undergoing this procedure (12%). In the rituximab era, results are even better because of the synergistic activity of the combination monoclonal antibody – chemotherapy. Despite good results, there still are some differences between patients undergoing autologous stem cell transplantation ant those who do not. If general consensus exists for diseases like Hodgkin lymphoma or diffuse large B cell lymphoma, for other types of lymphoproliferative disorders, like indolent lymphomas, there still are controversies, especially after the advent of targeted therapies.

The classic treatment of lymphoma evolved in a spectacular manner during the last 50 years. Some important data are noteworthy: during the 60's the apparition of anthracyclins, the concept of autologous stem cell transplantation during the 70's, in the 90's the concept of targeted therapy and the first monoclonal antibody – rituximab. All of the above changed the vision on lymphoid malignancies from lethal to potentially curable diseases.
Despite all this changes, there still are some lymphomas in which current therapies do not allow for the obtention of a real cure, but only of remissions, more or less long.
The actual level of knowledge regarding mechanisms of lymphomagenesis should allow developing new therapies that will have a better targeted action on malignant cells with less side effects.
During the last decade, a new way evolved into the treatment of lymphoma: immunotherapy. This procedure could be active or passive, the purpose being the complete eradication of minimal residual disease, without important toxicities. The understanding of intimate mechanisms of action of monoclonal antibodies results into a logical attempt of improvement of their function. The mechanisms that allow the destruction of target cell could be: ADCC, direct toxicity, CDC and a possible vaccine effect.

Hypothesis

Our study follows the results obtained by Nagler and al; following autologous stem cell transplantation, we associate Rituximab, a monoclonal antibody to interferon alpha and interleukin 2 to obtain a passive immunotherapy. The anti-tumor effect of Rituximab in the treatment of B-cell lymphomas was very well proven in a large number of studies. The mechanism of action of this monoclonal antibody is multifactorial: the modulation of the influx/efflux of calcium into the cell, CDC, ADCC.

For our study we considered patients treated for lymphoma in condition of minimal residual disease, namely post autologous stem cell transplantation. The patients underwent passive immunotherapy which consisted in four weekly perfusions of rituximab followed by two blocks of 7 weeks of the association interferon alpha – interleukin 2. We compared the results to a standard population which did not have immunotherapy. We evaluated first for all patients and then for the subclasses of lymphoma the disease-free survival and the overall survival. A long follow up of patients was necessary for the accurate results of the study.

Patients and methods

Between 2000 and 2003 we identified 64 patients with lymphoma, who underwent autologous stem cell transplantation in Brest Transplantation Unit, France.
The diagnosis of lymphoma was made using up to date standards on a biopsy fragment. To describe the type of lymphoma we used cytological, immunophenotypical and cytogenetic analysis classically recommended by WHO consensus 2005.
To measure the extent of the disease we used CT scan, bone marrow aspirate and lumbar puncture. Stage was defined according to the Ann-Arbor system. In concerned patients the prognostic scores IPI and FLIPI were calculated but no statistical analyses were made using these items.
Final diagnosis was formulated using the WHO 2005 recommendations.
The patients underwent adapted treatment for each type of lymphoma, using the recommendations of the French Society of Hematology (SFH). The evaluation of response was made using the same parameters as for the diagnosis and were expressed using the Cheason criteria described 1999.
Then the patients underwent autologous stem cell transplantation in Brest transplantation Unit. Before autograft, the patients were evaluated for infection, and hepatic, renal and cardiac function. Prevention of nausea was made by Zophren and Plitican. All patients had hyperhydration through a central veinous catheter.
The conditioning regimen was BEAM (BCNU, Etoposid, Aracytine and Melphalan) or CBV-Novantrone (Cyclophosphamide, BCNU, Etoposide and Mitoxantrone).
After the graft, the patients had four weekly perfusions of Rituximab at 375 mg/sqm followed by two cycles of seven weeks of interferon alpha and interleukin 2. The doses of these drugs were 1,5 million IU of interferon daily and 6 million IU of interleukin daily.
Between the characteristics of patients receiving and those who did not receive immunotherapy, there are no statistically significant differences.

Results

Five years analysis shows:

- There are differences between patients receiving immunotherapy and those not receiving this consolidation therapy: disease-free survival is 75% for the first group and 44% in the second
- Overall survival was 81% for the patients with immunotherapy and 56% for the patients not receiving it

These results confirm results obtained by Nagler and al. and other published data. Performing post autologous stem cell transplantation immunotherapy in patients treated for lymphoma, all type of lymphoma included, allows obtaining better overall and disease free survival. These results became obvious at five years analysis. Regarding relapses, they tend to appear in the first years after the treatment, time representing a very important prognostic factor.
We then analyzed the different types of lymphomas that showed CD20 antigen positivity: follicular lymphoma, diffuse large B cell lymphoma, and mantle cell lymphoma. Unfortunately, because of the limited number of patients, it is not possible to perform accurate statistical analysis. We will perform in this case only a descriptive analysis of each subgroup.

Discussion

The data on the antitumor effect of interferon alpha and interleukin 2, already available, shows there is an additive effect of the two molecules. After the graft procedure, the levels of interleukin 2 remain very low for a period up to 18 months. The diminution of circulating levels of this cytokine, with important function in stimulating and proliferation of cellular immunity, rise serious problems regarding the reconstruction of the natural antitumor activity and for the efficacy of the defense system. Reinjection of interleukin 2, immediately post autograft, allows for the obtaining of circulating levels of this cytokine close to normal, which compensate, at least partially the low antitumor effect induced by the autograft procedure. In this way we tried to reduce the risk of reactivation of lymphoid stem cells, the main mechanism of the relapse. The mechanism by which

interleukin 2 eliminates the residual disease is speeding the recovery of the lymphocytes LAK and NK, and, on the long run, the recovery of effectors CD4 and CD8. The association of interleukin 2 to interferon alpha, allows enhancing the expression of histocompatibility antigens type 1 or 2 at the surface of the cells, enhancing the presentation by dendritic cells of the lymphoma antigens, creating in this way a better target for effectors activated by interleukin 2.
Immunosuppression status induced by the autograft procedure could last for 18 months or longer. In this period there is a higher susceptibility to bacterial or viral infections. Immunologic recovery is a gradual process with a highly variable period. The recovery of cell cytotoxic toxicity, mediated by the lymphocytes of NK type, CD16 CD56, is available starting two weeks after the autograft. The process of NK recovery could be accelerated, in vitro, by the administration of interleukin 2 and interferon; the effect of this accelerated recovery is a higher antitumor ADCC effect on the lymphoma cells, previously targeted by Rituximab.
In our case we found an accelerated immunologic recovery by the administration of the combination Rituximab, interferon alpha and interleukin 2. Our results confirm the results previously reported by Nagler et al. We found a lower risk of relapse, and an enhanced disease-free survival and overall survival for the patients treated by this triple immunotherapy. Adverse events of this therapy are relatively minor, reversible and transient.
Our results confirm the favourable effect of the administration of immunotherapy by rituximab, interferon alpha and interleukin 2, in situation of minimal residual disease, in post autologous stem cell transplantation, in the treatment of patients with non-Hodgkin's lymphoma. Ideally, our results will have to be confirmed by larger, randomized studies.

Conclusion

Analyzing results obtained in the two cohorts of patients, we observe that administration of triple immunotherapy in the situation of minimal residual disease, in post autologous stem cell transplantation, allows for the improvement of the good results obtained with the autograft procedure. These results are obvious regarding disease free and overall survival. For the patients undergoing immunotherapy and relapsing, we found that the relapses were less aggressive. Despite the low number of patients treated with immunotherapy we found interesting results in patients in the subgroups of diffuse large B cell lymphoma, follicular lymphoma and transformed follicular lymphoma.
Our work, despite a limited number of patients, confirms results already published, and opens a new path for the treatment of lymphoma: passive immunotherapy by the association of rituximab, interleukin 2 and interferon alpha, for the patients treated for non-Hodgkin's lymphoma, in the situation of minimal residual disease, post autologous stem cell transplantation.

Curriculum Vitae

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Publications-books: "Atlas des gestes techniques en hematologie", booklet for doctors and nurses, published and distributed for free in the Grand Ouest region of France

Papers:

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