TREATMENT OF THE PERIPHERAL T LYMPHOMAS (PTCL)

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Abstract: *PTCL is a heterogeneous group of diseases, each with a disappointing rate of healing; therapeutic progress is slow for this rare disease. Development of molecular biology techniques lead to better knowledge of these disease subtypes regarding the pathogenesis and thus it may be obtained new therapeutic targets. Prospective multicenter clinical trials remain critical to determine the best therapeutic regimens that can improve the cure rate for this aggressive disease. The existence of other comorbidities with T lymphoma gives an extremely poor prognosis requiring adaptation and improvement of therapeutic regimens.*

Cuvinte cheie: *PTCL, tratament, imunoterapie*

Rezumat: *PTCL reprezintă un grup heterogen de boli, fiecare cu rată dezamăgitoare de vindecare, progresele terapeutice se fac încet pentru bolile acestea rare. Dezvoltarea tehnicilor de biologie moleculară duce la cunoaşterea mai bună a acestor subtipuri de boli în ceea ce priveşte patogenia şi astfel se pot obţine ţinte terapeutice noi. Trialuri clinice prospective multicentrice rămân de importanţă majoră pentru determinarea celor mai bune regimuri terapeutice ce pot îmbunătăţi rata de vindecare în această agresivă boală. Existenţa altor comorbidităţi cu limfoamele T conferă un prognostic extrem de prost necesitând adaptarea şi îmbunătăţirea regimurilor terapeutice.*

INTRODUCTION

PTCL treatment includes prophylactic treatment for NHL HTLV positive and a curative one. It is based on 1) general measures, 2) chemotherapy (standard doses or high doses, maintenance chemotherapy, chemotherapy in relapse/resistance to therapy), 3) radiotherapy 4) biological modulators, 5) antiretroviral therapy, 6) monoclonal antibodies therapy, 7) prospects for gene therapy, 8) surgical measures.

Prophilactic treatment for HTLV infection No treatment currently exists to eradicate the HTLV virus; that is why prophylaxis, prevention, patient education are necessary. The virus is transmitted through blood, semen, vaginal fluids, breast milk. Among those infected with HTLV 1-90% are carriers and only 1-4% can make the adult T-cell lymphoma or tropical spastic paraparesis. Breast feeding is not recommended in order to prevent infection of newborns - in countries that adopted this health policy HTLV infection decreased dramatically. An important role is played by prevention of sexual and drug use transmission as well as screening for detection of HTLV antibodies in blood donors. HTLV Vaccination is directed against Tax gene sequence with prophylactic and therapeutic target.

1. Treatment of opportunist infections prophilactic and/or curative is as important as the treatment of hematologic disease itself: Biseptol for Pneumocistis Carini infection, ganciclovir for Citomegalovirus, treatment/prophylaxis of zona zoster infection, herpes simplex, fungal or bacterial infections. The appearance of infections is determined both by immune suppressed status and treatment of disease that leads to haematologic depression.(1)

Diet is important for patients with cancer / lymphoma; nutrient content (vitamins, minerals, proteins, carbohydrates, fats, water) must be adequate. Gastrointestinal side effects of chemotherapy can make it hard the proper feeding. They may occur through disease involving the digestive tract, as a side effect of chemotherapy treatment or superimposed infections; appetite, smell, absorbtion, food digestion may be affected leading in many cases to malnutrition, fatigue, failure to resist infections and to control therapy. There are needed guidelines for healthy feeding suitable for patients with cancer.

Radiotherapy is integrated in the therapeutic plan of many patients with T lymphomas parallel with chemotherapy because most T lymphomas are in advanced stages of the disease, stage III and IV. It can be used as monotherapy just in cutaneous and nasal forms. Patients with mediastinal localization have also a therapeutic benefit.(2)

Immunotherapy is recently investigated and used in addition to conventional chemotherapy. The answer to this is to be evaluated. Immunotherapy in lymphoma is a new and exciting area of research in the last 10 years. It uses modified T cells multiplied, re-infused, directed against tumor cells. (3,4,5,6,7)

Alemtuzumab – human monoclonal antibody directed against CD52 – CD52 is present on the majority of malignant T cells, which makes it an attractive target for PTCL. Spread on the normal T and B cells, monocytes, macrophages leads to profound immunosuppression with restriction of combination with other chemotherapies. Its use as a single agent for pretreated patients with PTCL gave an overall response rate of 36%, but half of patients treated with alemtuzumab developed CMV reactivation. Encouraging results suggest that the combination of alemtuzumab with chemotherapy is feasable but high toxicity remains a major limitation of its use. It is necessary prophylaxis with valaciclovir 500 mg/day, diflucan 200 mg/day, Biseptol 2 tb/day three times a week including 2 months after therapy. (8)

*AntiCD30 antibodies(*9), *anti CCR 4 antibodies,*

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HUMAX- CD4 (10)*HeFi1*, *anti CD64 antibodies* (11) *pralatrexat*, *monoclonal antibodies*, *antireceptor of human transferine(mAbA 24)* (12), proteinkinase C modulators and bryostatin proved to be efficient in refractory/relapsed T NHL. (13,14)

The effect of **antitumor vaccines** directed against the idiotypic TCR in cutaneous T lymphomas Involvement of tumor suppressor genes in the pathogenesis of pT represents a potential candidate for molecular target therapy; gene therapy uses adenoviral vectors to mediate gene p53 transfer (15,3,4,5,6)

2. Chemotherapy: Standard therapeutic regimen CHOP type (cyclophosphamide750mg/m^2, vincristin 1,4mg/m^2, Farmorubicin 50mg/m^2 day 1, Prednisone 40mg/m^2 days 1-5) is maintained as basic therapy in T lymphomas but with disappointing results with the exception of ALCL. Large trials compare CHOP with **chemotherapeutic regimens of IInd and IIIrd generation**. Following regimens can be used DHAP, ASHAP, PitMiCEBO, mBACOD, ACVB, NCVB, VCAP-AMP-VECP, VIM, ACVM, CTVP, protocole LNH 87, hyperCHOP, MBACOS, MINE, hyperCVAD, CHOP+ Etoposid + Gemsar (16,6). The results suggest that the high toxicity regimens must be balanced with higher rate of complete responses. Agents as paclitaxel, topotecan, flavopiridol may be modulators of kinase-dependent cyclin with activity in hematologic malignancies, particularly NK lymphomas.

Nucleoside analogues have proven effective in these subtypes of lymphomas in the few studies performed. *Fludarabine, pentostatine Litak* are purine analogues that inhibit adenosine deamination, the enzyme highly concentrated in T lymphoid cells, phosphorylated derivatives of analogues induce apoptosis and decrease ribonucleotide reductase and inhibition of replication and DNA repair. They are used in micosys fungoides and PTCL with cutaneous determination. Gemcitabine, pirimidinic antimetabolite, used in relapse of PTCL as single agent or in combination with other agents, gave favorable responses in several studies performed in PTCL and MF (18). *Compound 506u78*, oxicoguanozine analogue, was used in PTCL, but grade 3-4 neurotoxicity and drug-related early mortality limit its use. (19)

Danileukin difitox (ONTAK), approved by the U.S. since 2000, is a fusion protein between interleukin-2 molecules and peptide sequences of the active enzyme and translocated domain of diphtheria toxin membrane and is targeted interleukin 2 receptor on T cells. It is used effectively for cutaneous T lymphoma, in relapsed PTCL. Side effects: nausea, vomiting, fever, pseudoflu syndrome, allergic reactions, infusion related events: dyspnea, back pain, hypotension, hepatocytolisis. There are administered 2 doses of Ontak at 3 weeks.: 9 or 18 mg / kg / day, 5 days.(20)

B**axoter, Bexarotene (Targretin, LGD 1069)** is an oral agent, a synthetic selective retinoic agonist approved in 2007 by the U.S. FDA for patients with refractory / relapsed micosys fungoides and in other cutaneous T lymphomas. Side effects are: hypertriglyceridemia, fatigue, pruritus, leukopenia, rash. There is also a form of topical gel application

Inhibitors of deacetylated histones Acetylated histones modulates gene expression, cell differentiation, survival and are regulated by histonacetiltransferase and histondeacetilase (HDAC). HDAC inhibition gives rise to acetylated nucleosomal histones which induce apoptosis in transformed cells, decreasing cell proliferation. (14) **Depsipeptides, Daclizumab** (registered in October 2007) **Vorinostat** (21,22)- have demonstrated activity in relapsed PTCL with an overall response rate of 26%. **Nelarabin (deoxiguanosin derivative)** was recently approved for children whith T cell leukemia, lymphoblastic lymphoma (42), in ATLL and aggressive NK cell lymphomas and in LGL (large granular cell).

Bone marrow transplant (BMT) The role of autologous and allogenic bone marrow transplant in T lymphomas is not well defined. BMT role in first relapse is accepted that the standard. High doses of chemotherapy are followed by bone marrow transplant. It is used to extend survival in PTCL. Several small trials await the demonstration of the role of high doses chemotherapy followed by stem cells transplant. The studies are quite difficult to interpret due to heterogeneity of lymphomas' subtypes. **The answer is different** depending on the type of transplant (allo or auto transplant), the time of administration (primitive or lymphoma in relapse or refractory to salvage therapy), and depending on whether or not the pediatric cases are included.(23,24) In the absence of randomized trials, using high dose chemotherapy and stem cell transplant as first line treatment has shown superiority over conventional therapy. Patients with relapse, who showed initial chemosensitivity, respond favorably to high-dose chemotherapy and stem cell transplant with long-term survival rate of **35-54%.** The outcome of patients with **refractory** PTCL is less favorable with low long-term survival rate, although other reports reveal a 5 year survival rate of **37%**. Resistance mechanisms are due to the rise of multidrug-resistance and to suppression of gene P53. (15)

The success rate varies with the pre-transplant IPI (international prognostic index) and histological subtype so ALCL demonstrate their superiority in response rate and survival compared with PTCLUS. However favorable results for patients with ALK + ALCL does not extend to cases ALK-. BMT in T / NK lymphomas can be used as part of salvage therapy in chemosensitive patients in relapse. In ATLL, allogenic BMT was perfected in a few patients with inconsistent results due to problems of HTLV eradication.

Allogenic stem cells transplant in PTCL was performed on some small series of highly selected patients.
Mortality with treatment is greater in patients receiving allogenic transplant after fully myeloablative regimen. (25) Reduction of conditioning intensity is an attractive strategy for patients at increased risk of treatment toxicity, but this can not be used in patients with aggressive lymphoma because it would decrease the response rate. The response was improved after leukocytes infusion from the donor by increasing graft effect versus lymphoma.

Antiviral therapy: **interferon-α and zidovudine** combination results in an average survival of 11-18 months with an initial response rate of 70-90% in patients with T lymphoma and especially in those with ATLL detected with HTLV positive. Another combination was **interferon α and Combivir** (Zidovudine + Lamivudine). In general, it is choose concomitant chemotherapy and antiviral therapy using antiviral monotherapy in maintenance treatment for an indefinite period in general or determined by viremia evolution under treatment.

There are several **treatment procedures established for MF / SS**: topical therapy using skin applications of cytostatic agents or fluorinated corticosteroids; **Photochemotherapy** uses 8 methoxypsoralen orally that accumulate in the skin where it is decomposed by ultraviolet light (PUVA). (26)

For localized lymphomas, intestinal lymphomas, **surgery** remains the basic treatment; appropriate reduction of tumor mass has repercussions on response to treatment and therefore on survival.

In general in T lymphoma it can not be used monotherapy being either surgery, radiation or antiviral therapy; instead a comprehensive treatment must be adopted including in

general chemotherapy, adjusting treatment according to patient's performance status, taking into account the results of international studies, experience, patient compliance, drug availability in the country, the possibility of enrollment in clinical studies.

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