

Artigo / Article

## T- Lymphoblastic lymphoma in adults

### *Linfoma linfoblástico T dos adultos*

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*Adult T-lymphoblastic lymphoma is rare and has a poor prognosis. In the 80s, following the introduction of sequential, intensified chemotherapy, complete remissions in the order of 75%-95% of treated patients, were achieved. However, several patients, namely those with advanced disease, continued to relapse either in remission or during maintenance therapy. Moreover, all these early studies were not able to detect any valuable prognostic index to predict the outcome. In an attempt to reduce the relapse rate, upfront autologous stem cell transplantation in patients in complete remission was introduced. The results obtained with this approach were quite homogeneous, indicating a probability of disease-free survival of about 65%-75% and an overall survival rate of 60%. Successive therapies designed since 2000 were able to obtain complete remissions of above 90%, with a relapse rate in the order of 30% and an overall survival comparable to that obtained with the transplant procedure. Yet, these studies were also unable to detect valuable prognostic factors predictive of the outcome. Moreover, no study on the biologic profile of the disease has been developed. To improve the prognosis of T-lymphoblastic lymphoma it seems necessary to create national registries to collect both clinical and biological data of all lymphoblastic lymphoma patients. In this way it will be possible to reach critical numbers of data with which valid statistical analysis may be performed that is able to detect factors influencing the outcome. Moreover, subsets of patients needing intensified procedures such as stem cell transplant may be detected at diagnosis. Rev. bras. hematol. hemoter. 2008; 30(Supl. 2):45-49.*

**Key words:** T- Lymphoblastic Lymphoma; autologous stem cell transplantation, intensified chemotherapy.

### Introduction and conventional treatment

Adult lymphoblastic lymphoma (LBL) is a rare disease which represents about 2% of all non-Hodgkin lymphomas (NHL). T phenotype is the most common one, amounting above 80%-90% of all types of LBL.<sup>1</sup> T-LBL is an aggressive disease, more frequently occurring in adolescents and young adult males, frequently with mediastinal involvement at diagnosis. Bone marrow involvement is also common during the course of the disease often with a rapid progression leading to an overt leukemia-like disease. CNS involvement

is also very frequent. The disease at presentation is often at Stage IV with morphologic and phenotypic aspects similar to acute T lymphoblastic leukemia (T-ALL) even though in T-ALL cells are mainly pre-thymic while in T-LBL cells mostly originate from the cortex and medulla of the thymus.

Clinically these two entities remain undefined and definition thereof varies among the various Centers.

Due to the rarity of the disease treatment of adult LBL remains to be standardized and up to now only few controlled trials have been developed, in general with a poor number of patients. Initial studies involving first and second line

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protocols designed for NHL reported overall survival at 3-5 years of 10-15%.<sup>2,3</sup> Between 1970 and 1980 more intensive protocols were employed in the children with a dramatic improvement of the outcome.<sup>4,5</sup> These protocols involve an intensive induction therapy with CNS prophylaxis, followed by a consolidation therapy and maintenance therapy. In 1976 Wollner *et al* reported a probability of overall survival of 76% with a median observation of 25 months in young patients treated with intensified sequential poly-chemotherapy.<sup>6</sup> Similar results were confirmed in 2003,<sup>7</sup> however, other authors were not able to confirm these results in patients with advanced disease.<sup>8</sup>

In the light of the above results, intensified sequential therapies were adopted in adults with LBL. Exploiting protocols similar to those used in acute ALL, complete remissions (CR) in the order of 70-95% with 40% to 60% of patients achieving long-term disease free survival (DFS) were obtained.<sup>9-13</sup>

The major draw-back of these therapies became evident soon after, mainly in that patients in advanced stage (IV) continued to relapse for about three years, either during or off therapy. A series of negative factors seemed to influence both freedom from relapse (FFR) and overall survival (OS), the most probable ones being stage IV, CNS involvement, bone marrow involvement and LDH above 150% of normal values.

In 2002 Hoelzer *et al.* published the results of two different therapeutic protocols used both in patients with T-LBL and T-ALL.<sup>14</sup> In this study patients were defined T-LBL if marrow involvement was <25%. In terms of response, 42/45 patients (93%) obtained a CR and 2 patients (4%) a PR. Complete remission was 100% in stage I-III and 89% in stage IV patients. Thirty-six per cent of the patients relapsed with a 7-year OS and DFS of 62% and 51%, respectively. Mediastinum relapse was the most frequent event in spite of the radiotherapy. The AA concluded that it is possible to obtain a high percentage of CR when intensive protocols designed for ALL are employed. Mediastinum irradiation was strongly recommended. No negative prognostic factors were detected from this study. In the final comments, autologous stem-cell transplantation was also recommended.

In 2004 the Houston Group published the results obtained in LBL with a drug combination called hyper-CVAD.<sup>15</sup> In this study 33 patients were treated with two similar therapeutic protocols lasting about 36 months: 80% of the patients were T-LBL, 70% were in stage IV, 70% had mediastinum involvement, 9% CNS involvement and 15% bone marrow involvement <25%. Complete remission was achieved by the 91% while 9% had a PR. At a median observation of 13 months, 30% of the patients relapsed. Actuarial survival curves of T-LBL show a probability of OS and progression-free survival (PFS) of 67% and 62% respectively. No potential negative prognostic factor had modified the outcome. Final observations were that the

addition of anthracycline to the original protocol did not improve the outcome and that the use of monoclonal antibodies and/or purine analogues is recommended.

The most striking observation of these first phase studies was that therapeutic evolution has markedly improved the CR probability, but this fact did not translate into a significative improvement of the outcome. Probably this is due to several negative prognostic factors, so far not clearly defined, most likely due to the low number of patients studied. Probably advanced stage and bone marrow involvement are the most important negative factors. The relapse rate, in the last studies around 30%-40%, seems independent from the status of the patient (in CR or in maintenance therapy). The above mentioned results are obtained with a therapy lasting between 1 and 3 years and such a long treatment period heavily affects the QOL of the patients

### Role of hemopoietic stem cell transplant

Even though intensified (or ALL-like) therapies have modified both CR and outcome rate of adult LBL, long term OS is still unsatisfactory in several series of patients, being around 50%-60%. Moreover, several patients relapse. As such, high dose therapy followed by autologous stem cell rescue (ASCT) or allogeneic stem cell transplantation (Allo-SCT) were utilized to consolidate first CR after conventional CT.

Available data suggest that an induction-consolidation therapy followed by autologous or allo-SCT may improve the outcome in LBL, however, which subset of patients could benefit from this procedure is still under discussion.

A number of studies referring to 343 patients treated with autologous SCT<sup>16-27</sup> and 59 patients treated with allogeneic SCT<sup>16,24-28</sup> show a probability of long-term DFS of 65% (range 31-77) and of OS of 63% (range 39-91), respectively.

Autologous SCT shows a favourable trend in terms of DFS as compared to conventional CT, however, it does not statistically improve the OS. This observation was obtained by the randomized study of the European Group that compared conventional chemotherapy and ASCT in 65 patients with LBL who had responded to a conventional induction-consolidation therapy.<sup>26</sup> The most important results of this study, confirming the reports of phase II studies, were:

- Patients treated with conventional chemotherapy continue to relapse for about 3 years, while patients treated with ASCT relapse in the first year (RFS 55% vs 24%,  $p=0.06$ ).
- OS is similar (ASCT, 56%; CT, 45%;  $p=0.70$ ) because patients relapsing after conventional CT can undergo ABMT as salvage therapy.
- Negative prognostic factors able to select a subset of patients in which HD therapy followed by ASCT rescue could be beneficial, were not detected.

- OS, according to IPI adjusted for age, shows a statistical significant difference in disfavour of patients with 3 prognostic factors at diagnosis (OS < 10%; p = 0.01)

- OS of 12 patients who underwent allo-SCT is 58%, comparable to what observed with the ASCT.

Allo-SCT in first CR is characterized by a DFS similar to that obtained with the ASCT: in fact with ASCT relapses are higher; on the other hand Allo-SCT shows a much higher toxicity and mortality (TRM), resulting in DFS similar with both procedures.<sup>27</sup>

Later studies published by EBMT Group in 2003,<sup>29</sup> by several successive studies published by the French Group in 2003<sup>30</sup> and by the Japanese in 2006 and Canadian Study Group in 2007<sup>31,32</sup> did not modify the previously reported conclusions.

To summarize, Allo-SCT should be used in selected cases or following ASCT failure.

Prognosis is obviously worse for patients transplanted in other situations (progressive or persistent disease, > 1st CR).

### Negative prognostic factors

Available data on LBL studies are statistically meagre due to the rarity of the disease. Therefore, statistical studies of negative prognostic factors led to different results, sometimes contradictory and by no means conclusive.

For the Stanford Group, CNS+, BM+, increased LDH, stage IV were statistically important. Mazza and co-workers found that B symptoms, Bulky disease and BM involvement were important negative factors; age >30 years was significant for Clarkson *et al*; stage IV for the Pavia Group.

However, the above mentioned, more relevant studies<sup>14,15</sup> did not confirm these aspects. Also the European randomized study comparing CT and ASCT,<sup>26</sup> did not detect negative prognostic factors able to predict the outcome in the adult LBL.

Definition of high risk patients should be important however, because such patients should be ideal candidates for intensive therapies, including SCT or experimental approaches.

### Morphologic, immunologic and genetic analysis

T-LBL frequently occurs at the level of the anterior mediastinum (thymic) even though it can involve any nodal or extra nodal site (skin, tonsils, liver, spleen, CNS and testis). Pleural effusion is also frequent. Lymphoblast cells are medium sized and have a high nuclear-to-cytoplasmic ratio, dispersed chromatin, inconspicuous nucleoli and thin nuclear membrane. The cytoplasm is sparse and variably basophilic. Nodes generally present complete disorganisation of the normal architecture with infiltration of the capsula and infiltration of adipose interlobular tissue.

T-lineage cells have surface CD7 and cytoplasmic CD3 (cCD3) antigens. More than 90% of the T lymphoblasts express CD1a, CD2, CD5 and TdT. CD7, CD4 and/or CD8 are variably expressed. Other variably expressed molecules are CD99 e CD34. In 29%-48% of the cases there is nuclear expression of TAL-1.

T-lineage ALL/LBL can be divided into three stages of immunophenotypic differentiation:

Early (CD7+, cCD3+, surface CD3-, CD4+, CD8+ and CD1+) mid or common (cCD3+, surface CD3-, CD4+, CD8+ and CD1+) and late (surface CD3+, Cd1- and either CD4+ or CD8+). It is to be noted that T-LBL more frequently belong to the more mature subset (cortical and medulla) as compared to the T-ALL, that more often are pro-T and pre-T.<sup>33</sup>

In T-ALL/LBL T cell receptor genes almost invariably show monoclonal re-arrangement. In 20% of the cases there is a contemporary rearrangement of the Ig genes. An abnormal karyotype is present in about 50%-70% of the cases. The most common cytogenetic abnormalities involve TCR loci and transcriptional factors.<sup>34</sup>

The most important deletion is del (9p) that determines the loss of suppressor gene CDKN2A. Lastly, in about 50% of the cases there are mutations involving NOTCH 1 gene which encodes for a protein fundamental for the initial maturation of the lymphocyte. A recent study has demonstrated that the NOTCH 1 gene mutation is associated with the worst outcome in adult but not childhood T-ALL patients.<sup>35</sup>

More recently gene expression profile (GEP) studies involving the use of DNA micro-arrays were able to detect some gene signatures corresponding to specific maturation stages observed during the development of normal thymocytes.<sup>36</sup> A number of other GEP based studies have identified several gene prognostic factors; however the majority of such studies were done on pediatric patients while nothing was done in the adult on this matter.

### Conclusions

In conclusion, up to now prognostic models, based either on clinical or molecular biology data, for the outcome of LBL or to judge the best therapeutic option (i.e. High-Dose Therapies and Stem Cell Transplants) are not available. Therefore, the Italian Intergroup for Non-Hodgkin's Lymphoma (IIL) is starting a new approach including:

- 1) a study on a vast case number basis able to ascertain whether and which "clinical" prognostic factors exist able to define "high risk patients";

- 2) a phenotype study of LBL and of "leukemia-like" LBL to ascertain whether a possible phenotype characteristic could represent a negative prognostic factor;

- 3) a gene profile study with the micro array technique, as already done in T-ALL to detect new prognostic markers in T-LBL;

4) a PCR study to monitor MRD (TCR gene rearrangements) as a remission parameters, which is so far lacking in T-LBL.

5) a PET scan study which could be a useful prognostic element for the definition of "high-risk patients".<sup>37</sup>

### Resumo

*O linfoma linfoblástico de célula T é raro e com prognóstico ruim. Após introdução de terapêutica quimioterápica seqüencial e intensificada, remissões completas passaram a ser obtidas em 75%-95% dos pacientes. Entretanto, muitos pacientes, particularmente aqueles com a chamada doença avançada, continuaram a recair tanto durante a terapia de indução como na manutenção. Além disso, todos estes estudos iniciais não foram capazes de detectar qualquer índice prognóstico capaz de prever a evolução dos pacientes. No sentido de reduzir as taxas de recidiva, o transplante autólogo de célula progenitora hematopoética em pacientes em remissão completa foi introduzido. Os resultados obtidos com esta abordagem foram bastante homogêneos, indicando uma probabilidade de sobrevida livre de doença de 65%-75% e uma sobrevida global de 60%. Sucessivos tratamentos desenhados já nos anos 2000, foram capazes de obter remissões completas acima de 90%, com taxas de recidivas da ordem de 30% e uma sobrevida global comparável à obtida com o transplante. Ainda, estes estudos também não foram capazes de detectar fatores prognósticos relacionados à evolução válidos. Mais ainda, qualquer estudo com perfil biológico foi desenvolvido. Para melhorar o prognóstico do LLB-T parece ser necessário esforço multicêntrico, de caráter nacional ou internacional, para coletar dados clínicos e biológicos. Nesta linha, é possível alcançar número crítico de dados com valor estatístico que poderiam ser capazes de detectar fatores com influência prognóstica. Finalmente, grupos de pacientes necessitam ser identificados para selecionar aqueles que poderiam se beneficiar do transplante de célula progenitora hematopoética detectados ao diagnóstico. Rev. bras. hematol. hemoter. 2008; 30(Supl. 2):45-49.*

**Palavras-chave:** Linfoma linfoblástico T; transplante autólogo de medula óssea; quimioterapia intensificada.

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