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# Monocytosis has adverse prognostic significance and impacts survival in patients with T-cell lymphomas

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ABSTRACT

In this retrospective study we evaluated the prognostic impact of peripheral blood monocytosis in patients with T-cell non Hodgkin lymphomas with "aggressive-typically nodal presentation". In this dataset monocytes >0.8 × $10^9$/L had a strong and statistically significant negative impact on overall survival (OS).

In univariate analysis several parameters, including age >60 years, advanced stage, bone marrow involvement, ECOG PS >1, high LDH level, monocytes >0.8 × $10^9$/L, hemoglobin < 120 g/L, albumin < 35 g/L) had a negative influence on outcome, but in multivariate analysis, monocytosis alone had a stronger association with poor OS.



## 1. Introduction

Peripheral T-cell lymphomas (PTCL), a heterogeneous group of neoplasms, with a different pathogenesis, variable clinical course and response to therapy [1–3], account for 10–15% of all non-Hodgkin lymphoma [2,3]. They are usually clinically aggressive tumors and patients with PTCL generally respond poorly to treatment, commonly relapse and have a dismal prognosis and outcome [1]. In contrast to their B-cell counterpart diffuse large B-cell lymphoma (DLBCL), general consensus and an optimal therapeutic approach for PTCL has not yet been reached. There is as yet no single internationally accepted risk stratification score, and therapeutic issues remain both problematic and challenging. In this respect, the International Prognostic Index (IPI), originally described in 1993 [4] to grade aggressive lymphomas, is still used to stratify PTCL, however, it's predictive impact still needs to be improved. Because of this, some newer alternative scoring models created specifically for PTCL, have been introduced including the Prognostic Index for T-cell lymphomas (PIT score) [5], a modified PIT (m-PIT) [6], and a scoring model suggested by the International Peripheral T-cell lymphoma Project (IPTCLP) [7].

In recent years it has become apparent that the invasive properties of malignant cells per se are not the only factors involved in tumorigenesis and that the development and growth of lymphoid neoplasms also depends on a variety of components in the surrounding tumor microenvironment [8]. Neoplastic cells interact with a mixture of inflammatory and immune cells present in the surrounding stroma, with production of chemokines and cytokines which affect cell proliferation and survival, and subsequent tumor growth. As a result, some of the scoring systems now available for PTCL have attempted to integrate a few of the well recognized surrogate bio-markers into novel scoring models [9–12]. Some parameters are indeed readily available laboratory data and include the most frequently reported value such as absolute lymphocyte count, serum albumin, chemokine receptor and serum-soluble interleukin-2 receptor (sIL-2R) levels [11,13–15].

Recently, several groups have demonstrated that analysis of another simple parameter, the absolute peripheral blood monocyte count (AMC) can also be used as a reliable prognostic value in DLBCL

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[16–18], follicular non Hodgkin lymphoma (FL) [19] and Hodgkin lymphoma (HL) [20]. Some observations obtained from analysis of monocytes and macrophages and related biological features have emerged, reporting their immunosuppressive role during tumorigenesis [21,22]. In addition, a sub-population of monocytic-myeloid derived suppressor cells (MDSc) has also been recognized and characterized in the peripheral blood of patients with hematological malignancies including lymphomas [17,23,24] and may also play a role in tumor growth.

In this study, we recorded the AMC in patients with newly diagnosed PTCL with "aggressive-typically nodal presentation" and attempted to determine whether monocyte count $>0.8 \times 10^9$/L, could be utilized as a simple prognostic parameter for survival, as reported for other B-cell lymphomas and HL. The AMC was also compared to other more conventional prognostic factors and predictive models for T-cell lymphomas, including the IPI, and PIT score.

## 2. Design and methods

### 2.1. Patients

In this retrospective analysis of previously untreated patients with aggressive T-cell lymphoma data were retrieved from the archives of the Modena Cancer Registry (MCR) and the Gruppo Italiano Studio Linfomi (GISL). The MCR collects detailed clinical and survival data on patients with lymphoma resident in the province of Modena, Italy. Cases were taken from the MCR archives after obtaining formal approval from the MCR ethical board. Patients registered in the GISL archive had been enrolled in clinical trials that complied with the requirements of the Declaration of Helsinki and its amendments. These studies were conducted in accordance with Good Clinical Practice guidelines and included patients after obtaining written informed consent. In this retrospective study there was no central pathology review, however the diagnostic histopathological criteria for defining T-cell lymphoma were uniformly applied; since 2002, combined meetings between pathologists working within the GISL were held to standardize diagnostic criteria and diagnosis collected by the MCR were performed by at least two pathologists working together as a team, collaborating with the GISL pathologist group.

During the period 1988–2011, 94 cases with PTCL with "aggressive-typically nodal presentation", and available data on monocyte counts at diagnosis, were recorded. Of the 94 patients, 32 (34%) received combination chemotherapy containing cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens; 33 (35%) were treated with methylprednisolone, cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine and methotrexate (ProMaCE-CytaBOM = PCB regimen); 10 (11%) received other chemotherapy regimens, while in 19 patients (20%), details regarding treatment were incomplete or unavailable.

### 2.2. Statistical analysis

The end-point used for evaluation of the prognostic role of monocyte count, was the overall survival (OS). OS was measured from the date of diagnosis until the last follow-up or date of death from any cause. Categorical covariates were reported as a proportion and continuous covariates were given as a median value with a range of their values. Comparisons between categorical and continuous covariates were performed with the Fisher's exact test or $chi^2$ test or the Mann Whitney test respectively. OS was assessed by the Kaplan–Meier estimates [25] and compared by risk groups using the log-rank test and the Cox proportional hazard (PH) [26]. The PH assumption was verified graphically by means of scaled Schoenfeld residuals [27]. The effect size was reported as Hazard ratio (HR) with the associated confidence interval at 95% (95%CI). If the curves crossed, we used the Renyi type test in addition to the log-rank test [28]. We did not plan a sample size for this study and $P < 0.05$ was considered sufficient to represent a moderate strength of evidence against the null hypothesis. This cut-off was helpful for detecting clinically useful findings. All tests reported are two-sided.

We tested several cut-off points for AMC including $0.63 \times 10^9$/L and $1 \times 10^9$/L as proposed by Wilcox et al. [16] and Porrata et al. [18], and Tadmor et al. [17], respectively. Furthermore, we examined an AMC of $0.8 \times 10^9$/L which had emerged from an earlier Israeli study on diffuse large B cell lymphoma [29]. This cut-off point showed the best performance in our database, on the basis of log-rank test, HR and Wald test from Cox PH regression and the receiver operating characteristic (ROC) curve analysis at 5-years of follow-up. Moreover, $0.8 \times 10^9$/L represent one of the most used upper normal limit for AMC and this value could be applied more readily and utilized worldwide.

The IPI score for aggressive non-Hodgkin lymphoma (NHL), which takes into account age >60 years, lactate dehydrogenase (LDH) level greater than the upper limit of normal (ULN), Eastern Cooperative Oncology Group performance status (ECOG PS) score >1, clinical stage III or IV disease, and more than one extranodal site of disease, was calculated in 82 (87%) of the total patient cohort. The PIT score for aggressive T-cell lymphoma which takes into account an age >60 years, LDH level greater than the ULN, ECOG score >1, and bone marrow infiltrate was determined in 83 (88%) of the 94 cases.

## 3. Results

A total of 94 patients with PTCL diagnosed between 1988 and 2011 were entered in this retrospective study. Patients' characteristics are described in Table 1. The median age at diagnosis was 59 years (range 16–88) and 47% of the patients ($n = 44$) were >60 years. Most were male (71%, $n = 67$). The distribution by histopathologic subtypes was: 52% (49 cases) peripheral T-cell lymphoma not otherwise specified (PTCL NOS), 27% (25 cases) anaplastic large cell lymphoma (ALCL), 18% (17 cases) angioimmunoblastic T-cell lymphoma (AITL) and 3% other histology (2 intestinal T-cell lymphoma and 1 extranodal NK/T cell lymphoma). The majority of patients had stage IV disease (44%, $n = 40$) and 21% ($n = 19$) had localized stage I disease. B-symptoms were registered in 52% of patients ($n = 46$) but almost all had an ECOG PS less or equal to 1 (9% with ECOG PS >1). Regarding the prognostic scores, IPI and PIT, the distribution was: 44% for IPI 0–1, 22% for IPI 2, 20% for IPI 3, and 15% for IPI 4–5; for the PIT score 32% had score 0, 29% score 1, 39% score 2–3, confirming the prognostic significance of both these models (Fig. 1A and B). The median patients' follow-up was 30 months (range 1–160 months); 74 months for the 46 patients (49%) still alive at the time of this report, and 10 months for the 48 patients (51%) who had died. The 5-years OS was 51% (95%CI, 40–61%) with a median OS of 71 months (95%CI, 23–138 months) (Fig. 2).

There were no differences for hemoglobin, white blood cell count, monocytes count, albumin level, LDH, B-symptoms, ECOG PS, extranodal disease, bone marrow involvement and clinical stage, amongst the different histopathological subtypes of PTCL. Differences were observed only for age; with median ages of 64, 51 and 59 years for AITL, ALCL and PTCL NOS, respectively (Kruskal–Wallis, $P = 0.026$).

The prognostic value of monocytosis, was analyzed in this series of cases. Twenty-two patients (23%) had $>0.8 \times 10^9$/L monocytes; the median monocyte count was $0.495 \times 10^9$/L (range $0.03–3.48 \times 10^9$/L) and there were no significant differences in the different histopathological entities.