Peripheral T-cell lymphoma, not otherwise specified.

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Abstract

Peripheral T-cell lymphoma, not otherwise specified, is a broad category of biologically and clinically heterogeneous diseases, which can not be further classified into any other of the existing entities defined by the World Health Organization classification. Anthracycline-containing regimens, namely cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), nowadays represent the standard first-line treatment; for patients who achieve a satisfactory response, a consolidation by means of autologous stem cell transplantation may offer a greater chance of long-term survival. Several patients, however, display treatment refractoriness or relapse soon after obtaining a response, and just a few of them are suitable transplant candidates. This is why several new agents, with innovative mechanisms of action, have been investigated in this context: pralatrexate, romidepsin, belinostat and brentuximab vedotin have been approved for relapsed and refractory peripheral T-cell lymphomas based on their activity, although they do not significantly impact on survival rates. The incorporation of such new drugs within a CHOP backbone is under investigation, in order to enhance response rates, allow a higher proportion of patients to be transplanted in remission and prolong survival.
Introduction

Peripheral T-cell non-Hodgkin lymphoma (PTCL), not otherwise specified (NOS), is the most common PTCL subtype, accounting for at least 25% of PTCL.\textsuperscript{1,2} It mostly affects adult patients, with a median age at presentation of 60 years and with a male predominance. According to data from the International T-cell lymphoma project,\textsuperscript{2} the disease is equally spread in Europe and North America, whereas it shows a slightly lower prevalence in Asia (34.3%, 34.4% and 22.4% of PTCL, respectively). The nodal involvement is prevalent at diagnosis, although any organ can be affected, including bone marrow (22% of cases), liver, spleen and skin, also in combination with nodal disease. Advanced stage at presentation is common (around 70% of cases), with almost two-thirds of patients presenting with an intermediate to high International Prognostic Index (IPI).\textsuperscript{3}

New classification issues and molecular signature

PTCL-NOS is diagnosed on an exclusion basis as a disease whose features are not consistent with any of the other PTCL subtypes defined by the World Health Organization classification.\textsuperscript{1} With current immunophenotypic and molecular markers, in fact, about 30-50% of PTCL cases are not further classifiable and are categorized as PTCL-NOS.\textsuperscript{2} As a consequence, this disease is heterogeneous and displays a broad cytological spectrum and a multiplicity of molecular aspects.\textsuperscript{4-6}

Gene expression profiling has improved the diagnosis of PTCL and nowadays it allows a better classification within well-specified subgroups:\textsuperscript{4-7} about 15% of pathologically diagnosed PTCL-NOS can be reclassified as angioimmunoblastic T-cell lymphoma (AITL)\textsuperscript{8}, whereas in nearly 10% of cases a correct diagnosis of anaplastic large cell
lymphoma (ALCL) or extranodal NK/T-cell lymphoma can be ruled out. Moreover, genetic studies have shown that some recurrent genetic abnormalities of TET2, IDH2, DNMT3A, RHOA and CD28 mutations are observed in cases of PTCL-NOS that manifest a T-follicular helper phenotype (TFH), as it happens with AITL.\textsuperscript{9-11} for this reason, the former follicular variant of PTCL-NOS has been moved to the new TFH-lymphoma category in the 2016 WHO classification.\textsuperscript{12} Recurrent gene fusions of VAV1, which encodes a critical component of the T-cell receptor signaling, have been recently described in a relevant proportion of PTCL-NOS and ALCL,\textsuperscript{13} along with rearrangements of ITK with genes such as SYK, FER and ERBB4: this suggests their possible role in regulating cell growth and in ultimately driving T-cell lymphomagenesis,\textsuperscript{14} as well as representing potential targets for therapy to be extensively exploited in rationally designed clinical trials. TP63 rearrangements have also been recurrently found in PTCL-NOS and ALCL characterized by high proliferation indices and more severe prognosis.\textsuperscript{13,15}

Significant improvements have been made in delineating specific biological and prognostic subgroups within the PTCL-NOS spectrum. Iqbal \textit{et al} have demonstrated that two major molecular clusters can be identified:\textsuperscript{7} one group shows a high expression of GATA3 and an enrichment of gene signatures related to cell proliferation (MYC), mammalian target of rapamycin (mTOR) and β-catenin; the other group significantly expresses TBX21 (T-bet) and is enriched of IFN-γ and NF-κB-induced gene signatures.\textsuperscript{7} Moreover, a subset of cases within the second group demonstrates enhanced expression of transcripts associated with cytotoxic T-cells, probably representing the cytotoxic variant identified previously.\textsuperscript{5} The expression of GATA3 substantially excludes the TBX21 signature, and vice-versa, thus permitting a clear distinction between the two subgroups. Importantly, GATA3 expression confers a poor prognosis, with a 5-year overall survival
(OS) of 19%,\textsuperscript{7,16} whereas cases with a \textit{TBX21} signature display more favorable outcomes (5-year OS, 38%).\textsuperscript{7}

Dissimilarities also exist according to the expression of the surface CD30 antigen.\textsuperscript{17,18} CD30\textsuperscript{+}-PTCL-NOS show a significant downregulation of genes involved in T-cell differentiation/activation (like the surface antigens CD28, CD52, CD69 and the transcription factor NFATc2) and T-cell receptor signal transduction (like the tyrosin-kinases Lck, Fyn, Itk), while they display enhanced expression of transcription factors like JunB and MUM1/IRF4. The expression of these genes is similar between CD30\textsuperscript{+}-PTCL-NOS and ALK-ALCL, but a striking difference exists between CD30\textsuperscript{+} and CD30\textsuperscript{-} forms, the latter having just an opposite expression pattern.\textsuperscript{19} In other words, CD30\textsuperscript{+}-PTCL-NOS and ALK-ALCL are mostly intermingled with one another, reflecting similarities in terms of morphological appearance and gene expression. Conversely, CD30\textsuperscript{-}-PTCL-NOS are not only molecularly divergent, but they also show a different clinical behavior: their OS and progression-free (PFS) survival rates (24 and 10.5 months, respectively) are in fact clearly worse than what is seen in CD30\textsuperscript{+}-PTCL-NOS and ALCL (approximately 60%), although without statistical significance.\textsuperscript{19} The real prognostic significance of CD30 expression, however, still remains to be confirmed.

Despite the segregation of PTCL-NOS on the basis of the differential \textit{GATA3/TBX21} signature or in terms of CD30 expression appears clinically meaningful, the diagnostic refinement is not part of routine practice and has no impact on the decision of first line treatment.

\textbf{Prognostic scores}
Several prognostic scores have been proposed to provide a clinical stratification of PTCL-NOS patients\textsuperscript{20-23} (Table 1). The IPI, specifically designed for aggressive non-Hodgkin lymphoma, is also valid in T-cell neoplasms and can be determined using clinically-derived variables.\textsuperscript{20} It is significantly associated with treatment outcomes, which appear better for lower scores: patients with low score (0/1 prognostic factors) have a 36% 5-year failure-free survival (FFS) and a 50% 5-year OS, in contrast with those with high score (4/5 prognostic factors), whose 5-year overall survival is only 11%, with 9% FFS.\textsuperscript{24}

To better define the clinical outcomes of PTCL-NOS cases, newer scores have been specifically built up: the Prognostic Index for PTCL-NOS (PIT)\textsuperscript{21} and the modified PIT (m-PIT).\textsuperscript{22} They share age (>60 years), Eastern Cooperative Oncology Group (ECOG) performance status (>1) and lactate dehydrogenase (LDH) elevation with IPI; PIT also takes into account bone marrow infiltration, while m-PIT integrates the expression of the proliferation-associated protein Ki-67. A fourth prognostic index derived from the International T-cell Lymphoma Project (ITCLP) indicates age (>60 years), ECOG (>1) and thrombocytopenia (<150,000/mmc) as the three most relevant parameters in the stratification of PTCL-NOS patients\textsuperscript{23}. Importantly, all these prognostic scores have been validated in subpopulations treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or at least an anthracycline-containing regimen. The four scores divide PTCL-NOS patients in 3 (m-PIT, ITCLP) or 4 (IPI, PIT) prognostic categories: the lower-risk group, whatever score is used (score 0/1 for IPI and m-PIT, score 0 for PIT and ITCLP), emerges as a clearly separated category and shows better outcomes than all the other risk groups\textsuperscript{20-27} (Table 2). Whether the approach to lower-risk patients should be more conservative, however, is matter of discussion, since at least 60-70% of these patients are likely to relapse within the first 5 years.
The value of positron emission tomography scan in the management of the disease

$^{18}$F-fluorodeoxyglucose (FDG) avidity is less predictable in T-cell lymphomas than in B-cell counterparts, but it is known that up to 90% of nodal PTCL show FDG-avid lesions,$^{28}$ and both nodal and extranodal involvement can be detected upon positron emission tomography (PET). At present, no recommendations exist regarding routinary use of PET scan during disease staging and restaging. It is known from published data that PET is able to change the disease stage in nearly 5% of patients at diagnosis$^{29}$ as compared to computed tomography, but this change does not translate into any treatment alteration, since systemic chemotherapy in nodal PTCL is generally used regardless of tumor extent. However, a more accurate description of disease extent at diagnosis, in particular in terms of extranodal presentation, may prove useful in response assessment and follow-up evaluation, and may also convey some prognostic information, given that the involvement of liver or lung has proven to be related to a possible worse outcome.$^{30}$

PET positivity found at the end of induction treatment$^{30,31}$ and in patients who have received autologous stem cell transplantation (autoSCT) is a strong predictor of reduced survival,$^{32}$ and this seems particularly true for PTCL-NOS and AITL patients. On the contrary, uncertainty still exists on the role of interim PET evaluation during induction treatment. Some published experiences document that a negative interim scan (described in terms of the International Harmonization Project or applying the Deauville 5-point scale) has a favorable impact on OS$^{29,33}$ and maybe on progression-free survival (PFS),$^{34}$ possibly because PET-negative patients were more likely to receive consolidation therapy which contributed to their better survival rates. On the other hand, others show a lack of any prognostic value.$^{30}$
First line treatment

**Anthracycline-based induction regimens.** The main goal of first-line treatment should be the achievement of deep remissions and long-term control of the disease, if not a cure. Anthracycline-based regimens are considered the current standard of care in induction treatment of PTCL patients, as demonstrated in several reported experiences in which the CHOP combination was adopted in a proportion of patients variable from 60% to 85%.2,24,35-37 A meta-analysis by Abouyabis et al showed that anthracycline-based regimens used as an induction strategy in PTCL-NOS patients could induce a complete response (CR) in 17% to 70% of patients, according to different published series,38 however with a high rate of disease relapse or progression, yielding a 5-year OS of 32% to 45%.38 The International T-Cell Lymphoma Project failed to demonstrate any statistically significant survival advantage in terms of OS for PTCL-NOS patients receiving anthracyclines during induction over those who were treated with anthracycline-free regimens,2 as patients obtained 5-year FFS and OS of just 20% and 32%, respectively.24 The same trend was evident in a previously published report from the British Columbia Cancer Agency,35 where at least 75% of PTCL-NOS patients received CHOP chemotherapy and obtained a CR in 64% of cases, however with a 5-year PFS of only 29%. On the contrary, a more recent experience from Mayo Clinic and the University of Michigan showed superior outcomes in 326 patients with PTCL treated with anthracyclines during induction when compared to those who did not received anthracyclines: the difference remained significant when PTCL-NOS andAITL cases (191 patients) were extrapolated (median PFS and OS of 10 and 18 months for anthracycline-treated patients, versus <2 months in non-anthracycline-treated individuals) and when intermediate to high-
risk IPI cases were analyzed. Moreover, anthracycline-treated patients were more prone to receive a bone marrow transplantation, either in first or second remission.\(^3\)\(^9\)

More intensive chemotherapy regimens have not proven to be more effective than CHOP in historical controls;\(^3\)\(^8\) moreover, in a phase 3 randomized study by Simon et al, an alternative induction schedule including etoposide, ifosfamide, cisplatin, alternating with doxorubicin, bleomycin, vinblastine and dacarbazine (VIP-rABVD) did not show any superiority in terms of event-free survival (EFS) over CHOP (given every 21 days), thus confirming CHOP as the reference regimen for PTCL patients.\(^4\)\(^0\)

The role of the addition of etoposide to CHOP during induction was investigated in depth by the German High-Grade Non-Hodgkin Lymphoma Study Group:\(^4\)\(^1\) CHOEP, given either every 14 or 21 days, improved response and EFS rates in young patients with normal LDH levels (3-year EFS was 70.5% after CHOEP and 51.0% after CHOP, \(P=0.004\)), although 3-year OS did not significantly differ between the two groups (81.3% for CHOEP versus 75.2% for CHOP, \(P=0.285\)). More specifically, PTCL-NOS patients treated with CHOEP (22% of the patients) had a 3-year EFS and OS of 41.1% and 53.9%, respectively. Of note, attempts to improve outcomes in younger patients by escalating doses of any of the drugs included in CHOEP have failed. In addition, CHOEP failed to enhance clinical outcomes in patients older than 60 years, for whom CHOP should remain the standard first-line approach.

**Non-anthracycline-based induction regimens.** Besides CHOP, anthracycline-free combinations have also been tested as induction strategies in PTCL. The PEGS (cisplatin, etoposide, gemcitabine, methylprednisolone) regimen was conceived to use agents not effluxed by multidrug-resistance glycoprotein, whose expression confers chemotherapy resistance.\(^4\)\(^2\) In 26 patients treated first-line, the overall response rate (ORR) was 38% and the CR rate was 23%, which translated into a disappointing 2-year PFS of 14% and OS of
36%. Another gemcitabine-containing regimen, GEM-P (gemcitabine, cisplatin, methylprednisolone), previously tested in 16 relapsed or refractory PTCL patients, is now being evaluated in a randomized phase 2 trial, which involves CHOP chemotherapy as the control arm (NCT01719835).

**Frontline consolidation with autologous transplantation.** Given the short duration of remission and the high risk of relapse of PTCL patients responding to first-line treatment, frontline consolidation with autoSCT has been considered a valid therapeutic opportunity for patients achieving at least a partial response (PR) to induction.

Two prospective Italian phase 2 studies, reported together by Corradini *et al* and involving 62 patients with advanced stage PTCL, demonstrated a high CR rate (89%) after frontline autoSCT, with a 12-year OS, disease-free survival (DFS) and EFS of 34%, 55% and 30%, respectively. OS and EFS projections at 12 years obtained for the subgroup of PTCL-NOS patients (45% of the total) were 37% and 25%, respectively. More disappointing results emerged from a Spanish study which involved 41 PTCL treated upfront with intensified CHOP alternated with an etoposide, cisplatin, cytarabine and prednisone (ESHAP) regimen: 51% of the 24 transplanted patients were in CR after autoSCT, with 4-year OS and PFS of 39% and 30%, respectively, for the intention-to-treat population. This can be partly explained by the fact that this study specifically excluded ALK+-ALCL patients, whereas the previously reported Italian studies did not. Reimer *et al* reported the results of a prospective multicenter trial in which 83 patients (32 with PTCL-NOS) were treated with 6-8 CHOP cycles followed by mobilizing chemotherapy and total-body-irradiation+cyclophosphamide myeloablative therapy, with the rescue of autologous stem cells. Fifty-five patients were transplanted, with an intention-to-treat CR rate of 58% and an estimated 3-year OS of 48%, which increased to 71% if the only cohort of transplanted patient was considered. ALK+-ALCL patients were again excluded from the...
study. The Nordic Lymphoma Group applied a CHOEP induction strategy (given every 14 days), although omitting etoposide in patients over 60 years, in 160 PTCL patients (excluding ALK+-ALCL). The fifth or sixth cycle was used as a mobilizing therapy, while the upfront autoSCT was conditioned by carmustine, etoposide, cytarabine and melphalan (or high-dose cyclophosphamide). The reported CR rate was 51%; the 5-year OS and PFS were 51% and 44% for the entire patient population, respectively, whereas for PTCL-NOS patients 5-year OS and PFS were 47% and 38%. No differences in OS and PFS were noted between CHOEP and CHOP-treated subgroups, depending on patients’ age.

Taken together, these studies suggest that autoSCT consolidation seems to offer a greater chance of long-term survival in PTCL patients. Nevertheless, it should be noted that a substantial proportion of patients (16-41%) had evidence of progressive disease during induction or immediately before transplantation, thus precluding an effective consolidation in many instances. Moreover, no randomized trials have specifically clarified whether upfront autoSCT should be regarded superior to conventional chemotherapy.

**New drugs in relapsed disease**

As previously discussed, durable remissions are uncommon with anthracycline-containing regimens, particularly in patients with high-risk disease; moreover, autoSCT can not be performed in a significant proportion of patients, mainly because they do not obtain an adequate response or progress early. PTCL patients with recurrent disease display a dismal prognosis: their therapy represents an unmet medical need, as the best treatment strategy is yet to be determined. A study in 153 relapsed and refractory PTCL patients, including 79 PTCL-NOS, not candidate for autoSCT, documented a median OS and PFS after relapse of 5.5 months and 3.1 months, respectively, which were marginally
better for those who could receive chemotherapy at relapse (6.5 and 3.7 months, respectively; 6.5 and 3.8 months for PTCL-NOS).48

Combination chemotherapy (ifosfamide, platin or cytarabine-containing regimens) is sometimes used in younger and fitter patients, mostly as a bridge to autoSCT or allogeneic transplantation (alloSCT). However, responses are rarely seen in more than half of cases, their duration is short and CR is just occasional.49 Gemcitabine, used as single-agent in older and more vulnerable patients, has shown evidence of efficacy in PTCL-NOS patients who obtained a 55% ORR and a 30% CR rate.50

Four next-generation drugs (pralatrexate, romidepsin, brentuximab vedotin and belinostat) have recently been approved by the Food and Drug Administration (FDA) for the treatment of relapsed and refractory PTCL. Approvals were based on response rates alone, as none of these drugs has determined an increased OS: for this reason, European approvals of both pralatrexate and romidepsin have been rejected due to a lack of evident clinical benefit. Belinostat is not licensed in Europe, although it has been granted orphan designation status by the European Medicines agency. Brentuximab vedotin is solely approved for the treatment of relapsed or refractory systemic ALCL.

Given the overall rarity of each histologic subtype, it is important to remember that clinical trials specifically involving PTCL-NOS patients are lacking: outcomes obtained with new drugs will therefore be discussed for all the disease subgroups considered in each study; data on PTCL-NOS will be presented separately, when available (Table 3).

**Pralatrexate.** It is an intravenous antifolate agent with high affinity for the reduced folate carrier-1, which is responsible for its internalization; it also displays high affinity for folypolyglutamate synthase, which causes its polyglutamylation and retention within the cytoplasm, minimizing extrusion via cell membrane efflux pumps. Intracytoplasmic pralatrexate inhibits dihydrofolate reductase and thymidylate synthase, thus disrupting the
DNA and RNA synthesis required for cell proliferation. An early experience in patients with relapsed B- and T-cell malignancies indicated higher ORR rates in T-cell neoplasms (54% versus 31% for patients with B-cell lymphomas) and established its tolerability and efficacy on a weekly-based schedule. In the phase 2, single-arm PROPEL study, which involved 115 patients (111 received at least 1 dose) with relapsed or refractory PTCL, pralatrexate was administered as an intravenous bolus over 3-5 minutes at 30 mg/m²/week for 6 weeks, followed by 1 week of rest, until progressive disease or unacceptable toxicity. More than half of the enrolled patients were affected by PTCL-NOS, although all the most frequent subtypes were represented. The ORR was 29%, including 11% of patients with CR and 18% with PR; 32% of patients with PTCL-NOS responded. Nineteen percent of patients who had never achieved a response to any prior conventional therapy responded to pralatrexate, indicating the ability of this drug to overcome resistance. ORR raised to 35% among those who received only one prior systemic treatment, suggesting that the response rate might be better if this agent was used earlier in the course of the disease. The median PFS for the entire population was 3.5 months, with a median OS of 14.5 months. Mucositis was the most relevant adverse event, which determined dose reductions in 23% of patients and caused withdrawal from treatment in 6% of cases.

Romidepsin. It is a potent inhibitor of class 1 histone deacetylase (HDAC), given intravenously, that works inhibiting gene transcription by interfering with the acetylation pattern of histone lysine residues, which in turns regulates the structure of chromatin. The mechanism of action is complex and not fully understood, but its actions ultimately result in cell growth inhibition, cell cycle regulation and induction of apoptosis. It was firstly approved by FDA in 2009 for the treatment of patients with cutaneous T-cell lymphoma following at least one systemic treatment, while its activity was also demonstrated in
PTCL. A pivotal, open-label, phase 2 study in 130 relapsed or refractory PTCL patients, among which there were 69 PTCL-NOS cases, demonstrated an ORR of 25%, with 19% CR and with 29% of patients responding despite being refractory to their most recent prior systemic therapy. Twenty-nine percent of PTCL-NOS patients responded, obtaining a CR in 14% of cases. Responses were seen across all the most frequent histologies, although they were lacking in patients with rarer disease entities. The median PFS was 4 months for the entire cohort of patients, raising to 18 months for patients in CR, and OS was 11.3 months. Like other HDAC-inhibitors, side effects associated with romidepsin are predominantly hematologic, including neutropenia, lymphopenia, thrombocytopenia and anemia. Infections were commonly reported (55%), including upper respiratory tract and urinary infections, pneumonia and sepsis, mostly in concomitance with reduced white blood cell counts. Electrocardiographic changes have also been reported, although being not clinically relevant for patients without pre-existing cardiac abnormalities.

Given its efficacy as single agent, the role of romidepsin is now being explored in combination with conventional chemotherapy (gemcitabine, ifosfamide-containing regimens), lenalidomide (NCT01755975), pralatrexate (NCT01947140) and azacytidine (NCT01998035) in the setting of relapsed and refractory PTCL.

**Brentuximab vedotin.** It is an anti-CD30 chimeric antibody conjugated to a microtubule-disrupting agent (monomethyl auristatin E, MMAE) which is released by proteolytic cleavage once the antibody has bound to the surface antigen and has been internalized: MMAE blocks tubulin polymerization and alters the microtubule network within the cell, thus inducing cell cycle blockade and cell death. Its role in relapsed and refractory systemic ALCL patients is discussed elsewhere. Given that roughly 20-25% of PTCL-NOS express CD30 in at least 50% of tumor cells, the use of brentuximab vedotin seems rational in this category of patients. In a phase 2 study published by Horwitz et al,
35 patients with mature T-cell lymphoma with variable CD30 expression, among which there were 22 PTCL-NOS patients, were treated with brentuximab vedotin at the dose of 1.8 mg/kg every 3 weeks. Responses were seen in 41% of cases, including 33% of patients with PTCL-NOS (14% were CR), without any apparent correlation between CD30 expression and depth of response (responses were also seen in case of undetectable CD30 upon centralized pathological review). More recent data from the French named patient program experience in 56 patients with T-cell lymphomas, 11 of which had PTCL-NOS, confirmed a clinical response in 27% of PTCL-NOS patients, with CR obtained in just 18% of cases. Differently from the previously published experience, this paper indicates that a possible correlation between CD30 expression and response may exist: although the relationship between ORR and survival is influenced by histology, better responses to brentuximab vedotin were seen in those who displayed a higher CD30 expression, as documented by their better outcomes.

**Belinostat.** It is a hydroxamic acid-derived pan-HDAC inhibitor acting on all zinc-dependent HDAC enzymes. An early phase 2 experience demonstrated an ORR of 25% in pretreated PTCL patients, along with a favorable toxicity profile. The pivotal BELIEF trial in patients with relapsed or refractory PTCL involved 129 patients, more than half of them being affected by PTCL-NOS. Belinostat was administered intravenously at the dose of 1,000 mg/m² on days 1 to 5 every 3 weeks, and the treatment was continued until death or unacceptable toxicity. Meaningful responses were seen in 16% of patients refractory to their last prior systemic treatment, and notably in 23% of patients with PTCL-NOS. Median PFS was however only 1.6 months and the median OS was 7.9 months. In terms of safety, the most relevant adverse events observed within the study were nausea, fatigue and pyrexia, as well as anemia and thrombocytopenia.
**Investigational and off-label therapies.** Bendamustine, lenalidomide and alisertib are three agents displaying relevant activity in PTCL-NOS patients.

Bendamustine has been evaluated at the dose of 120 mg/m² (administered intravenously on days 1-2 every 3 weeks) in the phase 2 BENTLY trial of 60 patients with relapsed or refractory PTCL, including 23 patients with PTCL-NOS. Responses were seen across multiple histologies, including 41% ORR in PTCL-NOS, but their duration was short (3.5 months), lasting more than 1 year in only 7% of patients. Nevertheless, 2 patients could benefit of this treatment and had the chance to be allotransplanted.

Lenalidomide has been investigated as single agent in several trials involving pretreated PTCL patients, each enrolling a significant proportion of PTCL-NOS cases. The drug was administered at the oral starting dose of 25 mg per day, for 21 consecutive days on 28 days-based cycles. Responses rates varied between 22% and 30%, with CR rates ranging from 8% to 30%; specifically for PTCL-NOS patients, ORR varied from 20% to 43%. Response durations were short (3.6-5 months), although not substantially different than those reported for pralatrexate, romidepsin and belinostat. AITL, rather than PTCL-NOS or other PTCL subtypes, seems to be the context in which lenalidomide reaches its best performance.

Alisertib is a selective inhibitor of Aurora A kinase (AAK), a serine-threonine kinase that localizes to centrosomes from prophase through metaphase, controls the assembly of the mitotic spindle and regulates the mitotic process. AAK overexpression is appreciated in rapidly growing lymphoma subtypes and particularly in T-cell lymphoma. In a recently published phase 2 trial, alisertib given at the fixed oral dose of 50 mg twice daily for 7 consecutive days every 3 weeks produced an ORR of 24% in pretreated PTCL patients and of 31% in the PTCL-NOS subset. Responses were seen in patients who failed prior pralatrexate or HDAC-inhibitor treatment and in nearly half of those who showed disease...
refractoriness. Basing on these results, a phase 3 randomized trials comparing alisertib with investigator’s choice (gemoцитabine, pralatrexate, romidepsin) in relapsed or refractory PTCL patients is ongoing (NCT01482962): according to preliminary results, however, no significant efficacy benefit of alisertib versus comparators is documented.

Allogeneic transplantation

Reports on alloSCT in patients with T-cell lymphomas are rare and group together patients with very advanced and often refractory disease and several histology subgroups (Table 4). Therefore, it is hard to draw univocal conclusions about the real clinical impact of this procedure, and no clear discriminations can be operated for different disease subtypes.

The rationale behind alloSCT rests on the fact that allogeneic hematopoietic stem cells are free of tumor contamination and that donor-derived immune cells are potentially capable of mediating an antitumor effect. Disease status at transplantation and chemosensitivity are outcome predictors: a significant percentage of patients in remission at the time of transplantation can be cured of their disease and OS curves reach a plateau at approximately 18 months. On the contrary, only 25-30% of refractory patients may take advantage of the procedure: however, it should be noted that potential benefits of alloSCT in these patients can be the consequence of a potentially therapeutic graft-versus-lymphoma effect. No differences have been documented in relapse rates when a myeloablative regimen was compared to a reduced-intensity conditioning, although a higher rate of non-relapse mortality with myeloablative approaches still exists.

A direct comparison of autoSCT and alloSCT in patients with PTCL in first CR, PR or stable disease has been provided by the Autologous or Allogeneic Transplantation in T-
cell Lymphoma (AATT) randomized trial: after 4 courses of CHOEP (given every 14 days), patients were randomized to mobilizing chemotherapy and autoSCT or to alloSCT, provided they had a 10/10 HLA-matched donor. The pre-planned interim analysis on 58 evaluable patients showed no significant differences between the two transplant arms and no relevant improvement in terms of EFS in those allocated to the alloSCT procedure. Notably, 38% of randomized patients could not proceed to any transplantation because of early disease progression.

At present, alloSCT is feasible in just a few patients with relapsed PTCL, as most of cases are characterized by rapid progression, clinical decay and chemoresistance, all factors that may preclude a timely and effective application of this approach. Better OS and PFS results are obtained when alloSCT is performed early in the course of the disease and after a few treatment lines: this suggests that alloSCT should be performed as early as possible in patients with recurrent disease and preferably within a context of chemoresponsive disease.

**Moving forward from CHOP: new first-line “combo” steps**

Given that CHOP is regarded as the reference regimen for the induction treatment of patients with PTCL, it has been used as a backbone for new first-line combination regimens which incorporate drugs that have demonstrated their efficacy when used as single-agents in relapsed or refractory patients. New first-line “combo” steps are intended to enhance CR rates, to allow a higher proportion of patients to be autotransplanted in remission and to prolong survival. Phase 1-2 trials combining pralatrexate, romidepsin, belinostat and brentuximab vedotin with CHOP and CHOP-like regimens have recently been published and included PTCL-NOS patients. Randomized trials comparing new drug
combinations with CHOP are now ongoing (Table 5). The anti-CD52 monoclonal antibody, alemtuzumab, which worked well as single-agent in pretreated PTCL has also been investigated in combination with CHOP.

**Conclusions**

PTCL-NOS is a biologically and clinically heterogeneous disease. Anthracycline-containing regimens, mainly CHOP, followed by autoSCT in transplant-eligible patients are regarded as the standard, although the best first-line approach is yet to be defined. Several new drugs are active in relapsed and refractory patients, although they do not significantly impact on survival rates. Whether these drugs can be safely and efficiently combined with CHOP in newer first-line regimens is under investigation.
AUTHORSHIP

Contribution: A.B. and P.L.Z. conceived the work and wrote the paper.

Conflict-of-interest disclosure: The Authors declare no competing financial interests.

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REFERENCES


**Table 1.** Variables used in the calculation of relevant prognostic scores. IPI, International Prognostic Index; PIT, Prognostic Index for PTCL-NOS; m-PIT, modified PIT; ITCLP, International T-cell Lymphoma Project; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

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<td>Ann Arbor stage (III-IV)</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extranodal involvement (≥ 2 sites)</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (&lt; 150,000/mmc)</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki-67 (≥ 80%)</td>
<td></td>
<td></td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Comparison of IPI and PIT-calculated survival outcomes in four PTCL-NOS case series. Survival figures are given as percentages. IPI, International Prognostic Index; PIT, Prognostic Index for PTCL-NOS; OS, overall survival; FFS, failure-free survival; PFS, progression-free survival.

<table>
<thead>
<tr>
<th>Index</th>
<th>Score</th>
<th>Gallamini, 2004$^{21}$</th>
<th>Weisenburger, 2011$^{24}$</th>
<th>Ellin, 2014$^{25}$</th>
<th>Xu, 2015$^{26}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5-year OS</td>
<td>5-year OS</td>
<td>5-year FFS</td>
<td>5-year OS</td>
</tr>
<tr>
<td>IPI$^{20}$</td>
<td>low</td>
<td>0/1</td>
<td>59</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>low-intermediate</td>
<td>2</td>
<td>46</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>intermediate-high</td>
<td>3</td>
<td>40</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>4/5</td>
<td>18</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>PIT$^{21}$</td>
<td>group 1</td>
<td>0</td>
<td>62</td>
<td>50</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>group 2</td>
<td>1</td>
<td>53</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>group 3</td>
<td>2</td>
<td>33</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>group 4</td>
<td>3/4</td>
<td>18</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

(*) Low-intermediate and high-intermediate risk patients according to IPI are grouped together as intermediate risk patients.
Table 3. Selected experiences with approved single-agents and off-label compounds in peripheral T-cell lymphoma patients, including PTCL-NOS. ORR, overall response rate; CR, complete response; OS, overall survival; PFS, progression-free survival; mos, months; NA, not assessed.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Author, year</th>
<th>Pts.</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>Median OS, mos</th>
<th>Median PFS, mos</th>
<th>PTCL-NOS, N(%)</th>
<th>PTCL-NOS ORR, %</th>
<th>Toxicity‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralatrexate†</td>
<td>O'Connor, 2011</td>
<td>111</td>
<td>29</td>
<td>11</td>
<td>14.5</td>
<td>3.5</td>
<td>59 (53)</td>
<td>32</td>
<td>Mucositis, thrombocytopenia, nausea, fatigue, anemia, constipation, pyrexia, anemia, edema, cough, epistaxis, vomiting, neutropenia, diarrhea</td>
</tr>
<tr>
<td>Romidepsin†</td>
<td>Piekarz, 2011</td>
<td>47</td>
<td>38</td>
<td>18</td>
<td>NA (*)</td>
<td>NA (*)</td>
<td>27 (57)</td>
<td>41 (19) (**)</td>
<td>ECG T-wave changes, nausea, fatigue, thrombocytopenia, leukopenia, hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>Coiffier, 2012</td>
<td>130</td>
<td>25</td>
<td>15</td>
<td>NA (*)</td>
<td>4.0</td>
<td>69 (53)</td>
<td>29 (14) (**)</td>
<td>Nausea, asthenia/fatigue, thrombocytopenia, vomiting, diarrhea, pyrexia, neutropenia, constipation, anorexia, anemia, dysgeusia</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>Damaj, 2013</td>
<td>58</td>
<td>50</td>
<td>28</td>
<td>6.3</td>
<td>3.6</td>
<td>23 (40)</td>
<td>41</td>
<td>Neutropenia, thrombocytopenia, infections.</td>
</tr>
<tr>
<td></td>
<td>Zinzani, 2011</td>
<td>10</td>
<td>30</td>
<td>30</td>
<td>NA (*)</td>
<td>NA (*)</td>
<td>10 (100)</td>
<td>30 (30) (**)</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Morschhauser, 2013</td>
<td>54</td>
<td>22</td>
<td>11</td>
<td>NA (*)</td>
<td>2.5</td>
<td>20 (37)</td>
<td>20</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Toumishey, 2015</td>
<td>39 (***)</td>
<td>26</td>
<td>8</td>
<td>12.0</td>
<td>4.0</td>
<td>14 (36)</td>
<td>43 (14) (**)</td>
<td>Pain, fatigue, constipation, rash, diarrhea, anorexia, edema, nausea, anemia, dizziness, dyspnea, infection, insomnia, muscle weakness, thrombocytopenia, cough, pruritus</td>
</tr>
</tbody>
</table>

From www.bloodjournal.org by guest on September 14, 2017. For personal use only.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Source, Year</th>
<th>OS (%)</th>
<th>RR (%)</th>
<th>CR (%)</th>
<th>ORR (%)</th>
<th>CR (%) of PTCL-NOS (%)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin††</td>
<td>Horwitz, 2014</td>
<td>34</td>
<td>42</td>
<td>24</td>
<td>NA (*)</td>
<td>2.6</td>
<td>21 (62)</td>
</tr>
<tr>
<td>Belinostat†</td>
<td>O’Connor, 2015</td>
<td>129</td>
<td>23</td>
<td>9</td>
<td>7.9</td>
<td>1.6</td>
<td>77 (64)</td>
</tr>
<tr>
<td>Alisertib</td>
<td>Barr, 2015</td>
<td>37</td>
<td>24</td>
<td>5</td>
<td>8.0</td>
<td>3.0</td>
<td>13 (35)</td>
</tr>
</tbody>
</table>

† Toxic effects demonstrated in at least 20% of patients. †† Indicates that the drug has received a Food and Drug Administration approval in patients with relapsed and refractory peripheral T-cell lymphoma. †‡ Indicates that the drug has received a Food and Drug Administration approval in patients with CD30+ relapsed or refractory anaplastic large cell lymphoma. (*) OS/PFS evaluation was not an endpoint of the study. (**) The figure in brackets indicates the percentage of patients with PTCL-NOS obtaining a CR. (***) Includes 8 previously untreated patients not eligible for combination chemotherapy and 2 patients with lymphoblastic T-cell lymphoma.
Table 4. Allogeneic transplant experiences in patients with peripheral T-cell lymphoma including a significant proportion of PTCL-NOS patients. NRM, non-relapse mortality; CR, complete response; PFS, progression-free survival; OS, overall survival; MA, myeloablative; RIC, reduced intensity conditioning; NA, not assessed; NR, not reported; UNKN, unknown.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Pts.</th>
<th>Conditioning</th>
<th>NRM, %</th>
<th>CR, %</th>
<th>PFS, %</th>
<th>OS, %</th>
<th>PTCL-NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N (%)</td>
<td>CR, %</td>
<td>PFS, %</td>
<td>OS, %</td>
<td>Ref.</td>
</tr>
<tr>
<td>Le Gouill, 2008</td>
<td>77</td>
<td>MA: 74%</td>
<td>34 (5 years)</td>
<td>79</td>
<td>53 (*)</td>
<td>57 (5 years)</td>
<td>27 (35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RIC: 26%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobsen, 2011</td>
<td>52</td>
<td>MA: 60%</td>
<td>27 (3 years)</td>
<td>NA</td>
<td>30 (3 years)</td>
<td>41 (3 years)</td>
<td>20 (38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RIC: 40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dodero, 2012</td>
<td>52</td>
<td>RIC: 100%</td>
<td>12 (5 years)</td>
<td>NA</td>
<td>40 (5 years)</td>
<td>50 (5 years)</td>
<td>23 (44)</td>
</tr>
<tr>
<td>Smith, 2013</td>
<td>126</td>
<td>MA: 59%</td>
<td>34 (3 years)</td>
<td>NA</td>
<td>37 (3 years)</td>
<td>46 (3 years)</td>
<td>63 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RIC: 36%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>UNKN: 5%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

(*) It indicates event-free survival.
Table 5. Combination regimens including new agents for the first-line treatment of PTCL patients. AutoSCT, autologous transplantation; ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; MTD, maximum tolerated dose; MAD, maximum administered dose; FFS, failure-free survival; CMV, cytomegalovirus; EFS, event-free survival. Source: https://clinicaltrials.gov, accessed July 2016.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Phase</th>
<th>Study status</th>
<th>Study description</th>
<th>Available results</th>
<th>Ref. or NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralatrexate + CEOP</td>
<td>2</td>
<td>Completed</td>
<td>Alternation of CEOP (cyclophosphamide, etoposide, vincristine and prednisone) and pralatrexate in untreated patients with PTCL. AutoSCT permitted in transplant-eligible patients. Pralatrexate given at 30 mg/m² on day 15, 22, 29. Cycle duration: 6 weeks. 6 planned cycles.</td>
<td>33 patients enrolled; 64% PTCL-NOS. 45% of patients received autoSCT. ORR 70%; CR 52%; 2-year PFS 39%; 2-year OS 60%. PFS and OS not significantly improved if compared with reported data of CHOP and CHOEP.</td>
<td>81</td>
</tr>
<tr>
<td>Pralatrexate + CHOP</td>
<td>1</td>
<td>Ongoing</td>
<td>To find the MTD of pralatrexate in combination with CHOP in untreated PTCL. Up to 5 sequential escalating dose cohorts of pralatrexate (MAD: 30 mg/m²), given on day 1 and 8, together with CHOP. One expansion cohort with MTD of pralatrexate.</td>
<td>Final data collection for primary outcome measures: April 2017.</td>
<td>NCT02594267</td>
</tr>
<tr>
<td>Romidepsin + CHOP</td>
<td>1/2</td>
<td>Completed</td>
<td>To find the MTD of romidepsin in combination with CHOP in untreated PTCL. Three treatment cohorts of romidepsin (8, 10, 12 mg/m²) starting from 10 mg/m². One expansion cohort with MTD of romidepsin.</td>
<td>37 patients enrolled. Romidepsin MTD was 12 mg/m², given at day 1 and 8 every 3 weeks. ORR 68%; CR 51%; 18-months PFS 77%. Adverse events: hematological. Cardiovascular events observed, but questionable relationship with romidepsin.</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Ongoing</td>
<td>Randomized study to compare efficacy of romidepsin + CHOP versus CHOP in</td>
<td>Final data collection for primary outcome measures:</td>
<td>NCT01796002</td>
</tr>
<tr>
<td>Study</td>
<td>Cycle</td>
<td>Status</td>
<td>Primary Objective</td>
<td>Design Details</td>
<td>Primary Outcome Measures</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>------------------</td>
<td>----------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Romidepsin + CHOEP</td>
<td>1/2</td>
<td>Ongoing</td>
<td>To find the MTD of romidepsin in combination with CHOEP before autoSCT in young (&lt;65 years) untreated patients with PTCL. Four treatment cohorts of romidepsin (8, 10, 12, 14 mg/m²) starting from 12 mg/m². One expansion cohort with MTD of romidepsin.</td>
<td>Romidepsin given at 12 mg/m² on day 1 and 8 every 3 weeks. 6 planned cycles.</td>
<td>Final data collection for primary outcome measures: September 2017.</td>
</tr>
<tr>
<td>Belinostat + CHOP</td>
<td>1</td>
<td>Completed</td>
<td>To find the MTD of belinostat in combination with CHOP in untreated PTCL. Five treatment cohorts of belinostat, 1,000 mg/m² for 1 up to 5 days, together with CHOP, starting from cohort 3 (1,000 mg/m², days 1-3). One expansion cohort with MTD of belinostat.</td>
<td>23 patients enrolled. Belinostat MTD was 1,000 mg/m², days 1-5 (cohort 5). ORR (18 evaluable patients) 89%; CR 72%. Adverse events: those typically seen with CHOP chemotherapy.</td>
<td>Final data collection for primary outcome measures: December 2017.</td>
</tr>
<tr>
<td>Brentuximab + CHP</td>
<td>3</td>
<td>Ongoing</td>
<td>Double-blind, randomized, placebo-controlled study to compare efficacy of brentuximab vedotin + CHP (without vincristine to avoid excessive neurotoxicity) versus CHOP in CD30-positive mature T-cell lymphoma (ECHELON-2 trial).</td>
<td>Brentuximab + CHP versus CHOP.</td>
<td>Final data collection for primary outcome measures: December 2017.</td>
</tr>
<tr>
<td>Alemtuzumab + CHOP</td>
<td>2</td>
<td>Completed</td>
<td>Alemtuzumab given at 30 mg/cycle for the first 4 (part 1) or for 8 (part 2) cycles every 4 weeks in combination with CHOP in untreated patients with PTCL.</td>
<td>Alemtuzumab given at 30 mg/cycle for the first 4 (part 1) or for 8 (part 2) cycles every 4 weeks in combination with CHOP in untreated patients with PTCL.</td>
<td>24 patients enrolled; 58% PTCL-NOS. ORR 75%; CR 71% (50% for PTCL-NOS); 2-year FFS 48%; 2-year OS 53%. Relevant adverse events: infectious complications; CMV reactivation (9%).</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Completed</td>
<td>Alemtuzumab given at 90 mg/cycle for 8 cycles every 2 weeks in combination with CHOP in untreated patients with PTCL.</td>
<td>Alemtuzumab given at 90 mg/cycle for 8 cycles every 2 weeks in combination with CHOP in untreated patients with PTCL.</td>
<td>20 patients enrolled; 50% PTCL-NOS. ORR 90% (80% for PTCL-NOS); CR 65%; 2-year EFS 30% (10% for PTCL-NOS); 2-year OS 55% (30% for PTCL-NOS).</td>
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<td>---</td>
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<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ongoing</td>
<td>Randomized study to compare efficacy of alemtuzumab (A) + CHOP versus CHOP, followed by autoSCT, in young (&lt;60 years) untreated PTCL patients. Alemtuzumab given at the total dose of 360 mg (then of 120 mg after amendment for toxicity). CHOP given every 14 days for 6 planned cycles (ACT-1 trial)</td>
<td>Data presented for the first 68 patients. PTCL-NOS: 56% (A-CHOP) vs 55% (CHOP). Non-arm-specific 1-year PFS 54%; 1-year OS 78%. Estimated study completion date: December 2016. 88, NCT00646854</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Completed</td>
<td>Randomized study to compare efficacy of alemtuzumab (A) + CHOP versus CHOP in elderly (&gt;60 years) untreated PTCL patients. Alemtuzumab given at the total dose of 360 mg (then of 120 mg after amendment for toxicity). CHOP given every 14 days for 6 planned cycles (ACT-2 trial).</td>
<td>116 patients enrolled; 39% PTCL-NOS. CR 60% (A-CHOP) vs 43% (CHOP); 3-year PFS 26% (A-CHOP) vs 29% (CHOP); 3-year OS 38% (A-CHOP) vs 56% (CHOP). Differences in PFS and OS do not reach statistical significance. Survival not improved mostly due to treatment toxicity. 89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Peripheral T-cell lymphoma, not otherwise specified

Alessandro Broccoli and Pier Luigi Zinzani