Publications

Clinics of Oncology

Review article

Peripheral T-Cell Lymphomas: Progress in Treatment

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Volume 1 Issue 1 - 2018
Received Date: 20 May 2018
Accepted Date: 05 June 2018
Published Date: 07 June 2018

1. Abstract

Peripheral T-Cell Lymphomas (PTCL) arises from mature T-cells and they represent an extremely heterogeneous group. They are sub-classified into three major groups based on clinical presentation and localization, namely the nodal, extra nodal and leukemic PTCL. This review focuses on nodal PTCL which are the most frequently encountered entities. Nodal PTCL are divided into three basic categories: systemic anaplastic large-cell lymphoma (ALK+ sALCL and ALK- sALCL), Angioimmunoblastic T-cell Lymphoma (AITL) and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS).Nodal PTCL have a poor outcome with a 5-year Progression Free Survival (PFS) and Overall Survival (OS) of 25-38% and 30-45%, respectively. There is no standard treatment for these malignancies, so that the therapeutic strategy used in aggressive B-lymphomas has been adopted. Anthracycline-containing chemotherapy like CHOP is more often applied in the front line. The addition of etoposide to classic CHOP seems to favour patients under 60 years and especially those with ALK+ sALCL. Autologous Transplantation (ASCT) is used either as consolidation therapy following first complete remission or atrelapse after salvage chemotherapy. Allogeneic transplantation (allo-SCT) is an option usually after ASCT failure. Newer agents are investigated mainly in the relapsed/ refractory (R/R) setting, while the most active ones are being tested in front-line treatment, usually in combination with chemotherapy. These include nucleoside analogues (the main agent of this group is gemcitabine), antifolates such as plaratrexate and inhibitors of histone deacetylase like romidepsin and belinostat. Among the newer agents, Brentuximab Vedotin (BV) – an anti-CD30 antibody drug conjugate - has impressive activity in sALCL and has changed the dismal prognosis of R/R sALCL, especially ALK-. Lately, progress has been made in the understanding of the biology of PTCL. Therefore, new biological subsets have been identified which are characterized by activation of intracellular pathways offering new potential therapeutic targets. However, despite the plethora of new therapeutic agents, the natural history and prognosis of PTCL have not substantially improved yet. Hopefully, the understanding of the biological heterogeneity of these malignancies may enable a successful treatment approach. Multiple and overlapping pathways are possibly involved in the pathogenesis of these entities; clinical research should investigate the combination of chemotherapy with biological agents.

2. Introduction

Peripheral T-Cell Lymphomas (PTCL) develops from mature T-cells. They are extremely rare lymphomas and they represent an extremely heterogeneous group. According to World Health Organization [1], they are sub-classified into various entities based mainly on their clinical presentation and localization. With this system, twenty three different entities have been recognized [1], showing the lack of a true biological basis for their classification. There are three major categories of PTCL: nodal, extra nodal and leukemic. This review focuses on nodal PTCL which are the most frequent ones among PTCL and they are further subdivided into three basic categories: systemic anaplastic large-cell lymphoma (ALK+ sALCL and ALK- sALCL), Angioimmunoblas-

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Citation: Angelopoulou KM, John A, Iliana K, Vassilakopoulos PT, Tsourouflis G, Siakantaris PM and Konstantopoulos K. Peripheral T-Cell Lymphomas: Progress in Treatment. Clinics of Oncology. 2018; 1(1): 1-15

tic T-cell lymphoma (AITL) and peripheral T-Cell Lymphoma not otherwise specified (PTCL-NOS). Nodal PTCL are characterized by an unfavourable prognostic profile at diagnosis with extra nodal disease, advanced clinical stage, high LDH levels, B-symptoms, bone marrow involvement, poor performance status and hemophagocytic syndrome[2] **(Table 1)**. In contrast to other hematological malignancies, there has been minimal progress in the treatment of nodal PTCL as their biological basis of disease is not fully unravelled.

Table 1: Clinical features and outcomes of histologic groups of PTCL [2,14,15].

	sALCL ALK+	sALCL ALK-	PTCL-NOS	AITL
Median age (years)	34-41	50-67	5-69	64-70
Male (%)	54-63	61 -70	58-70	54-57
Clinical stage III/IV (%)	49-65	49-59	53-72	82-89
B-symptoms	54-75%	35-60%	40-61%	68-75%
Bone marrow involvement (%)	9-12	7-13	22	29 -36
IPI(%) (low/intermediate/high)	49-58/37-40/3-14	32-57/36-44/7-23	16-46/40-57/14-23	4-21/54-65/25-28
Special features	Subcutaneous Bones	Skin Liver Gastrointestinal system	Skin	AIHA, Hypergammaglobuli-nemia,
				Rash, Hepato-spleno-megaly,
				Effusions
5-year PFS/FFS/EFS (%)	60-75	31-38	20-35	18-28
5-year OS (%)	70-88	38-55	32-48	32-45

PTCL: Peripheral T-cell Lymphomas, ALK: Anaplastic Lymphoma Kinase, sALCL ALK+: ALK+ systemic anaplastic large cell lymphoma, sALCL ALK-: ALK- systemic anaplastic large cell lymphoma, PTCL-NOS: Peripheral T-Cell Lymphoma not otherwise specified, AITL: Angioimmunoblastic T-cell Lymphoma, IPI: International Prognostic Index, AIHA: Autoimmune Hemolytic Anemia, PFS: Progression Free Survival, FFS: Failure Free Survival, EFS: Event Free Survival, OS: Overall Survival.

3. Conventional Chemotherapy

Due to the rarity of these entities, there are no reliable data arising from randomized clinical studies that can define the optimum first line treatment. Therefore, treatment strategies that have been applied in aggressive B-cell lymphomas are mainly adopted. Thus CHOP or CHOP-like chemotherapy has been the mainstay of first-line PTCL treatment up to date. However, with conventional chemotherapy, PTCL have an inferior outcome compared to aggressive B-lymphomas with a 5-year progression free survival (PFS) and an Overall Survival (OS) 25-38% and 30-45% respectively [3-13]. ALK+ sALCL is the only exception with a 5-year PFS of approximately 60% and an OS of 70-85% [2,14,15]. Data from a retrospective analysis of 1320 patients with PTCL by the International T-cell Lymphoma Project are impressive. This analysis revealed that only patients with sALCL actually benefit from Anthracycline-containing chemotherapy [2]. Additionally, CHOEP may be more efficacious compared to classical CHOP for patient's ≤60 years with normal LDH, especially for ALK+ sALCL according to the subgroup analysis for PTCL within two large prospective randomized clinical trials from The German High-Grade Non-Hodgkin Lymphoma Study Group [15]. For patients older than 60years there was no benefit of CHOP-14 compared to classical CHOP-21[15]. In accordance with these results, two recent large registry studies from Sweden [6] and Czech Republic [16] have also shown the benefit of adding etoposide to standard Anthracycline-containing chemotherapy in patients≤60 years. The use of intensified chemotherapeutic combinations like ACVBP [17] of the GELA Group in which high dose anthracycline is applied or other combinations containing methotrexate, etoposide and ifosfamide like mBACOD [17], MINE [12], ESHAP [18] revealed no significant benefit. There is only one Mexican prospective randomized study focusing specifically on PTCL-NOS. In this study, including 227 patients with newly-diagnosed PTCL-NOS, CHOP was compared to an intensified regimen (CMED) consisting of methotrexate, high dose of cyclophosphamide, etoposide and dexamethasone [19]. PFS proved superior with CMED, but this regimen has not been adopted by the International Scientific Community. In conclusion, CHO(E)P remains the1st line treatment of choice, especially for ALK+ sALCL patients [2,14-16] or the ones with favourable prognostic features, such as patients with ALK- sALCL who are younger than 40years [20]or the ones with early stage disease and low IPI[2]. Such patients may achieve a relatively favourable outcome that is similar to ALK+ sALCL. More recently, it has been shown that ALK-sALCL patients, who carry the DUSP22 gene rearrangement found in approximately 1/3 of them, are also characterized by a favourable prognosis [21]. Unfortunately for the rest of PTCL patients, who represent the majority, treatment with CHO (E) P leads to a <30% chance of long-term disease control. High Dose Chemotherapy and Autologous Stem Cell Transplantation Autologous Stem Cell Transplantation (ASCT) are used either as consolidation therapy after achieving

first complete remission or in the Relapsed/Refractory (R/R) setting after salvage chemotherapy. ALK +sALCL patients should not be offered ASCT in first remission, since this subset is characterized by a favourable prognosis after initial treatment with conventional CHO (E) P chemotherapy. However, one should keep in mind, that ALK +sALCL patients with high IPI also have a compromised outcome with CHOP, achieving a PFS in the range of 25% [2]. For the rest of the patients, the results from retrospective [22-33] and prospective phase II [34-39] studies investigating the role of ASCT in 1st remission are controversial **(Tables 2 and 3)**.

Table 2: Prospective studies about ASCT in 1st complete remission in nodal PTCL.

	Corradini 2006[34]	**Reimer 2009/Wilhelm 2016[35,36]**	D'Amore 2012/2014	Rodriguez 2007[38]	Mercadal 2008[39]
Patients	62 (19 ALK+)	111, ALK-	166, ALK-	26, ALK-	41, ALK-
Median age (years)	43	46.5	57	44	47
First-line treatment	APO, DHAP,	CHOP,	CHO(E)P	Mega CHOP,	Mega-CHOP,
	MACOP-B,	Dexa-BEAM		IFE	ESHAP
Megatherapy	HDMTX/Mel	TBI/Cy	BEAM	BEAM	BEAM(C)
	HDAraC/Mito/Mel				
% of patients undergoing Mega-therapy	74%	68%	74%	77%	41%
CR/PR prior to ASCT (%)	56/16	48/18	49/30	61/16	49/10
OS	34% - 12years	44% -5years	51/41% - 5/10years	75% - 3years	39% -4years
PFS	30% - 12years	39% -5years	44/38% - 5/10years	53%	30% -4years
OS/PFS for Mega-therapy*	-/60%	71%	-	84%/56%	-
Median follow-up (months)	76	45	60.5	24	47

PTCL: Peripheral T-cell Lymphomas, ASCT: Autologous Stem Cell Transplantation, CR: Complete Remission, PR: Partial Remission, OS: Overall Survival, PFS: Progression Free Survival, *:Overall Survival/ Progression Free Survival for patients received Megatherapy, ALK: Anaplastic Lymphoma Kinase, APO: combination of vincristine, doxorubicin and prednisone, CHOP: combination of cyclophosphamide, doxorubicin, vincristine and prednisolone, CHO(E)P: addition of etoposide to CHOP combination, megaCHOP: combination of cyclophosphamide, doxorubicin, vincristine, etoposide and dexamethasone, DHAP: combination of dexamethasone, high dose cytarabine and cisplatin, BEAM: combination of carmustine, etoposide, cytarabine and melphalan, dexaBEAM: combination of dexamethasone and BEAM, BEAC: combination of carmustine, etoposide, cytarabine and cyclophosphamide, HDMTX/Mel: combination of high dose methotrexate and melphalan, HDAraC/Mito/Mel: combination of high dose cytarabine, mitoxantrone and melphalan, IFE: combination of ifosfamide and etoposide, MACOP-B: combination of methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin, TBI/Cy: combination of cyclophosphamide and total body irradiation.

Table 3: Retrospective studies about ASCT in nodal PTCL.

Author	Patients	Histologic subtype	Disease Status	5-year OS (%)	5-year PFS/EFS (%)
Vose et al. [23]	17	multiple	100% relapsed/refractory Chemo's: 21%, ChemoR: 10%	3-year: 35	3-year: 28
Fanin et al. [22]	64	ALCL	23%: 1st CR, 28%: 1st PR, ChemoR:40%	70	56
Blystad et al. [24]	40	PTCL-NOS: 50% ALCL: 35% AITL: 5%	28% 1st CR 100% Chemo's	58	48
Jantunen et al.[25]	37	PTCL-NOS: 38%	1st CR/PR: 49% 87% Chemo's	54	44
		ALCL: 30%			
Song et al.[26]	36	PTCL-NOS: 56% ALCL: 40% AITL: 5%	100% relapsed/ refractory 92% Chemo's	48	37
Angelopoulou 2003[27]	35	PTCL-NOS: 69% ALCL: 29%	14% 1st CR 75% Chemo's	33	26
Schetelig 2003[28]	29	AITL	48% 1st CR, 60% Chemo's	44	37
Kewalramani 2006[29]	24	PTCL-NOS: 58% ALCL ALK-: 17% AITL: 17%	100% relapsed/refractory 100% Chemo's (63%: 2nd CR)	24	33
Rodriguez2007 GELTAMO)[30]	123	PTCL-NOS: 57% ALCL: 25%	100% relapsed/ refractory 1st PR: 36%, Chemo's: 52%,	45	34
		AITL: 8%	ChemoR: 9%		
Yang DH 2009[33]	64	PTCL-NOS	1stCR: 25%, 1stPR: 19% ChemoS relapsed: 47%, ChemoR: 9%	3-year: 53	3-year: 44

PTCL: Peripheral T-cell Lymphomas, ASCT: Autologous Stem Cell Transplantation, OS: Overall Survival, PFS: Progression Free Survival, EFS: Event Free Survival, ALK: Anaplastic Lymphoma Kinase, ALCL: anaplastic large cell lymphoma, PTCL-NOS: PTCL not otherwise specified, AITL: angioimmunoblastic T-cell lymphoma, CR: complete response, PR: partial response, Chemo's: chemo sensitive, ChemoR: chemoresistant

It seems that Complete Response (CR) prior to ASCT is the most significant prognostic factor for successful outcome [39].Moreover, an impressively high proportion of patients fails to reach transplantation (23%-59%) due to early disease progression. Therefore, ASCT can offer cure in about 30-40% of patients in total [34-39]. Of course, the outcome is satisfactory for those who complete the program, as more than 60% of these patients achieve long-term disease control [34-36,38].Subgroup analysis within the German Mega CHOEP randomized study did not show superiority of CHOEP followed by ASCT over conventional CHOEP-14 for high-risk PTCL patients in first remission [13]. The French GELA Group came to a similar conclusion, but the number of patients with PTCL was very limited [40]. On the contrary, the Swedish registry study, showed superior PFS with ASCT in first remission [41]. These three aforementioned studies were not specifically designed for PTCL patients and indicate that no firm conclusions can be drawn whether ASCT in 1stCR should be the standard of care for all non ALK+ sALCL patients. Furthermore, a prospective randomized study focusing on PTCL and comparing ASCT versus allogeneic transplantation (allo-SCT) in 1st remission closed early due to in adequate patient accrual .Nevertheless, upfront ASCT is generally recommended for young patients with PTCL-NOS, AITL and ALK-sALCL, as well as those with high-risk ALK+ sALCL [36]. Evidently, most patients with nodal PTCL experience relapse or progression, while a significant proportion do have chemo refractory disease. The outcome of these patients is extremely poor, with no real chance for cure (median OS: 6.5 months), at least with conventional chemotherapy [42].The therapeutic strategies in R/R disease include salvage chemotherapy with regimens containing platinum and/or gemcitabine, followed by ASCT in responders. Chemo sensitivity and CR achievement are established as important factors for outcome, in contrast to chemo refractory patients, who cannot be salvaged by this strategy [25,27,31,32]. For patients under 65 years, with good performance status and response to second-line therapy, ASCT can offer long-term disease control to approximately 25-45% of them [23,26,29,31]. Even more, plateau in the survival curves is observed at 3 years, with rare late relapses. Allo-SCT is an option in the R/R setting, usually after ASCT failure in the extremely rare cases of chemo sensitive patients who are young and have good performance status. The existing retrospective studies indicate transplantation-related mortality rates ranging from 12 to 36% and long-term disease control in about 35-50% with a plateau at 2 years in the survival curves [43-47]. Once more, chemo sensitive patients have a favourable outcome, while allo-SCT can rescue 8-30% of chemorefractoryones [45-47]. It should be noted that these patients are highly selected and this strategy cannot be applied for the majority of the patients in every day clinical practice.

4. Novel therapeutic Agents

Newer agents are investigated mainly in the Relapsed/ Refractory (R/R) setting, while the most active ones are being tested in front-line treatment, usually in combination with chemotherapy.

4.1. Nucleoside analogs

Gemcitabine is a cytarabine analog and is the most effective agent of this group in nodal PTCL. Used as mono therapy, an Overall Response Rate (ORR) in the range of 60% and a CR rate ranging between 13% and 30% have been reported, with Duration of Response (DOR) extending one year [48-50]. Combinations of gemcitabine with cis-platinum and corticosteroids such as GEMP [51] and GDP [52], are suitable for salvage and mobilization of hematopoietic stem cells with high ORR, but rather short median DOR. An ongoing randomized study from the UK examines the efficacy of GEMP combination compared to CHOP in first-line therapy (NCT01719835). Bendamustine is a chemotherapeutic agent that combines alkylating with anti metabolite properties. In the BENTLY study, bendamustine was administered at a dose of 120mg/m2 for two days every 3 weeks in 60 patients with nodal PTCL (PTCL-NOS and AITL). The ORR and CR rate were 49% and 29% respectively, with extremely short median DOR of 3.5 months [53]. Similar results have been reported in two other series [54,55]. The most recent one is a multicenter retrospective study including 138 patients (PTCL-NOS: 40, AITL: 71, ALCL: 8). the median dose of bendamustine delivered was 90mg/m2. ORR and CR rates of 32.6% and 24.6%, a median DOR and a median PFS of 3.3 and 3.1 months were reported. Results were superior for AITL patients [55]. Therefore bendamustine seems to have rather limited efficacy in nodal PTCL.

4.2. Antifolates

Plaratrexate is similar to methotrexate in structure and mechanism of action, by inhibiting tetra hydro folate reductase, but it achieves much higher intracellular concentration. The Food and Drug Administration of United States (FDA) approved the use of the drug for patients with R/R PTCL in September 2011, based on the results of the PROPEL study [56].This study involved 111 patients (53% PTCL-NOS, 15% ALCL, 12% AITL) of whom 63% were refractory to the most recent prior chemotherapy. The drug dose was 30mg/m2/week for6 weeks followed by one week of rest (7-week cycle) with prophylactic administration of folic acid and

vitamin B12. The ORR and CR rates were 29% and 11% respectively. The median PFS was short (3.5 months), but the median DOR was 10.5 months. Mucositis was the most common adverse effect reported in 71% of the patients, grade 3-4 in 22%, while severe thrombocytopenia was observed in 33%. Due to limited effectiveness, adverse effects and no proof of clinical benefit, the Committee for Medicinal Products for Human Use of the US (CHMP) proposed a moratorium on the commercial use of the drug. Especially in the histologic category of AITL, the Committee recommended avoidance of its use. Currently there are only three ongoing clinical studies for pralatrexatein combination with other drugs, while the remaining ones closed.

4.3. Hidac inhibitors

Epigenetic aberrations, such as mutations in TET2, IDH and DNMT3 have been recognized in nodal PTCL [57,58]. Moreover, a number of Histone Deacetylases (HiDACs) are over expressed in PTCL and represent possible therapeutic targets. Inhibition of HiDACs causes acetylation of histone, resulting to tumor suppressor gene transcription and thus to apoptosis [59]. For nodal PTCL, two drugs of this category have been approved by the FDA: romidepsin (Istodax®) and belinostat (Beleodaq®). Romidepsin received approval for treatment of patients with PTCL following at least one prior treatment in 2011. This indication was based on a Phase II study in which 130 patients were enrolled, 69 had PTCL-NOS, 27 AITL and 21 ALK- sALCL [60,61]. Patients received romidepsin at a dose of 14mg/m2 as a 4-hour intravenous infusion on day 1, 8 and 15 of each 28-day cycle for at least six cycles. Although ORR and CR rates were notably low (25% and 15% respectively), median DOR was 28 months for all responders and had not been reached for those who achieved CR/ CRu. Moreover the quality of response had an impact on outcome: Complete responders whose responses lasted ≥12 months (53% of CRs), had a remarkable PFS of 29 months v_s 13 months for those whose CR lasted <12 months [61]. The histologic subtype of AITL seems to benefit the most from romidepsin with some responses lasting for >3 years [62].The favourable safety profile of the drug and its limited efficacy as mono therapy led to a series of studies investigating its combination with other agents. In a phase I/II study romidepsin was combined with CHOP in first line treatment at a dose of 12mg/m2. ORR was 69% and CR rate was 51%. After a median follow-up of 30 months, PFS and OS were 41% and 71% respectively [63]. The majority of patients tolerated the full dose of romidepsin. However there is a concern about cardiac adverse events. Currently, an ongoing phase III study is comparing the combination of romidepsin-CHOP with classic CHOP in first line treatment (NCT01796002). Other studies are investigating the effectiveness of romidepsin in combination with other chemotherapeutics like CHOEP, ICE, gemcitabine, pralatrexate and lenalidomide. Unfortunately, the in-vitro observed synergy between romidepsin and gemcitabine did not translate into the appropriate clinical benefit: in a phase 2 studies the combination of romidepsin and gemcitabine resulted in similar efficacy as romdepsin mono therapy but with additional hematologic toxicity [64].

Belinostat is the second agent of this group. It is an oral pan-inhibitor of HIDACs with anti neo plastic and anti angiogenic properties. The approval by the FDA in 2014 for the treatment of R/R PTCL was based on the data from the phase II study BELIEF [65]. This study involved 120 patients from 62 centres (64% PTCL-NOS, 18% AITL, 11% ALK-sASCL and 2% ALK +sASCL). The median number of prior treatments was two. Patients received belinostat at a dose of 1000mg/m2on days 1 to 5 every 21 days. ORR and CR were 26% and 11%, respectively, while median PFS and OS were reported as 1.6 and 7.9 months respectively. Although the efficacy of the drug seems to be limited, it is worth noting that similarly to romidepsin, the DOR for belinostat responders was particularly satisfactory (13.6 months) and that the drug has significant efficacy in the histologic category of AITL with 45.5% ORR. It was well tolerated and no serious adverse effects occurred expect from hematologic toxicity. Similar results regarding efficacy of belinostat were reported by another phase II study that enrolled 24 patients with PTCL [66]. Chidamide is another HIDAC inhibitor with modest activity that selectively inhibits activity of HDAC1, 2, 3 and 10. The Chinese Food and Drug Administration granted approval of chidamide in R/R PTCL in December 2014 [67]. The high frequency of TET-2 mutations found in 50-80% of patients with AITL gave the rationale for the application of the hypomethylting agent 5-azacytidine in this histologic entity. Impressively, 75% of AITL patients responded with a CR rate of 42%. More importantly 7/9 responders sustained their response at a median follow-up of 84 days [68].

4.4. Immunoconjugates

The main drug of this category is Brentuximab Vedotin (BV), also known as SGN-35 (Adcetris ®). It is an anti-CD30 antibody complex consisting of anti-CD30 conjugated with Monomethyl Auristatin E (MMAE) which is an anti neo plastic agent. The antibody is directed to the surface of cells that express CD30. After binding to the CD30 molecule, the drug is internalized by endocytosis and fused in lysosomes where MMAE is released. MMAE disrupts the microtubule network, damaging the mitotic spindle and leading to tumor cell death. BV is the fourth drug approved for nodal PTCL. In particular, it is indicated for the treatment of R/R sALCL that are CD30 positive by definition, in both USA and Europe. Currently it is approved only for the histologic group of sALCL, both ALK+ and ALK-. In contrast to the aforementioned novel agents, BV is highly effective, thus changing the unfavourable natural history of R/R sALCL, especially the ALK- and has become a crucial

component of treatment in the R/R setting. However it should be mentioned that ASCT must be the therapeutic target for chemo sensitive suitable patients in 1st relapse/progression, since it leads to long-term disease control in a substantial proportion of patients. The main study that underscored the efficacy of BV and led to its approval was a phase II trial involving 58 patients with R/R sALCL [69]. 72% of the patients had ALK-sALCL, 50% were refractory to their most recent therapy, 22% had not achieved objective response to any prior treatment and 26% experienced relapse after ASCT. The drug was administered at a dose of 1.8mg/kg, 180mg maximum dose, once every three weeks for up to 16 cycles. In these patients with highly unfauvorable characteristics, the results were impressive with an ORR of 86% and a CR of 57%. Impressively, outcome was independent of ALK status, chemo refractoriness and number of previous regimens. Complete resolution of all malignant cutaneous lesions occurred in 93% of the patient's with cutaneous lesions at baseline. Moreover, responses proved to be impressively durable according to the updated data: At a median follow-up of 3 years, PFS, DOR and duration of CR were 14.6, 13.2 and 26.3 months respectively [70], while, at four years of follow-up, median PFS reached 20 months with 64% of the patients being alive [71]. The corresponding survival curve indicates that a number of patients may be cured. Among the 38 patients who achieved CR, 19 (50%) were free of disease after a median follow-up of 46.7 months. Treatment with BV enabled 31% of the patients to undergo stem cell transplantation subsequently. The most recent update, namely the 5-year survival data indicate that results are sustainable: the 5-year PFS and OS are 39% and 60%, respectively [72].Real life experience with BV verifies that responses to BV are rapid and lasting with 5 long-term responders among 40 patients with R/R sALCL from an Italian multi-institutional study, although response rates were reported somewhat inferior to the ones from the pivotal study [73].BV has therefore led to a meaningful and clinically significant improvement in the treatment of sALCL. Historically, prior to the introduction of BV in the therapeutic armamentarium of sALCL, patients with R/R disease had poor outcomes with an OS of 7 and 12 months for ALK- and ALK+ patients respectively [74], while OS has been prolonged to over 5 years in the BV era [72]. The adverse events included neurotoxicity (57%) and bone marrow suppression, especially neutropenia (21%). In the majority of patients (81%) resolution or some improvement in neuropathy was observed, within 10 weeks with either dose delay or reduction to 1.2mg/kg. Further clinical applications of BV in PTCL are currently being investigated, such as 1) re-administration after initial response, 2) its use in other histologic types of PTCL that express CD30, and 3) its combination with chemo therapy in front line treatment. There are some interesting and promising results arising from recent clinical studies. Among 8 patients with sALCL in whom BV was reapplied, 7 responded, 5 achieved CR and the DOR had reached 12.9 months. Regarding the use of BV in other CD30+ entities except sALCL, results are heterogeneous and it should be noted that there is no standard definition of CD30 positivity by immune histo chemistry. The cut-off for defining a case as CD30+ is arbitrary and ranges from 5% to 30% of the tumor cells among authors. Moreover, CD30 expression varies across different histologic categories of PTCL and different investigators. Thus, positivity for CD30 is reported in 3-52% of PTCL-NOS and 0-21% of AITL. In a recent analysis, Bossard et al, attempted to examine the expression of CD30 using a semi quantitative method and revealed that 58% of PTCL-NOS and 63% of AITL were positive for CD30 at a 5% threshold. Intense positivity (>50% of cells) was found in 23% and 5% of PTCL-NOS and AITL respectively [75]. However, the correlation of CD30 expression and response to BV remains an open question. In a phase II study by Horwitz et al, BV was administered to 35 patients with other than anaplastic CD30+ nodal PTCL (22 PTCL-NOS, 13AITL). Patients with any detectable CD30 were eligible for the study. However, 17% of the patients had undetectable expression of the antigen by central pathology assessment. One third of patients with PTCL-NOS and over 50% of those with AITL achieved an objective response with a median DOR 7.6 and 5.5 months respectively. Strikingly, there was no apparent correlation between the expression of CD30 and the response to therapy. Responses were seen among patients with all levels of CD30 expression. In fact two of the responders had undetectable CD30. However, all patients had elevated levels of sCD30 at baseline [76]. The lack of correlation between CD30 expression and response to BV is puzzling and indicating limitations of immune histochemistry to detect very low levels of CD30. Another hypothesis may be local release of free drug from dying cells at an adequate concentration to kill adjacent tumor cells, even when a minority of the cells express CD30 antigen. Regarding the third new application of BV, its combination with CH (O) P in front line therapy of patients with CD30+ PTCL, preliminary data from a phase I study by Finale et al are promising [77]. The primary objective of the study was to assess the dose of BV in combination with CHOP. The study was designed in two arms. In the first arm (sequential administration), patients received two cycles of BV followed by six cycles of CHOP and 8 cycles of BV after the end of CHOP. In the second part (co-administration), patients received six cycles of BV in combination with CHP (vincristine was omitted), followed by ten cycles of BV alone. CD30 positivity was defined as ≥1% of malignant cells expressing CD30. The study involved 32 patients with sALCL and 7 with other CD30+

PTCL malignancies. Both arms were safe, while striking efficacy was reported (ORR: 100%, CR: 88%). Recently the updated results from this study have been reported after a median observation period of 52 months [78].The 4-year PFS and OS were 52% and 80% for the combination of BV+CHP, with 21/26 patients being alive at last follow-up. Based on these data, a phase III randomized study (ECHELON-2) is currently ongoing, investigating the possible superiority of BV and CHP combination over classical CHOP in first-line treatment for patients with CD30+ PTCL (NCT01777152). Immune toxin denileukin diftitox (Ontak®) also belongs to this therapeutic category. It is a genetically recombinant fusion protein consisting of the amino acid sequences of fragment A and B of diphteria toxin and sequences of human interleukin-2.The rationale of its use, is the fact that PTCL may express CD25 – the receptor for IL-2. According to phase II studies focusing on denileukin diftitox as mono therapy in PTCL, ORR was 48% [79], while patients with CD25+ expression had a higher objective response rate. Due to absence of hematologic toxicity, the drug was tested in combination with CHOP in front line therapy with favourable results [80]. Nevertheless, it has been withdrawn since 2011 due to serious adverse effects, such as capillary leak syndrome, infusion reactions, and visual loss [81].

4.5. Monoclonal antibodies

The first monoclonal antibody applied in PTCL is Alemtuzumab (MabCampath®). It is directed against CD52 antigen, which is expressed on the surface of B-cells, T-cells and monocytes. Therefore it is extremely immunosuppressive. As mono therapy it leads to short-living responses in about 36-50% of the patients [82,83]. Its efficacy has been tested in combination with pentostatin [84], Fludarabine/cyclophosphamide/doxorubicin [85] and DHAP [86]. Alemtuzumab has also been studied in various dosage schedules in combination with CHOP in first-line setting [81,87-91]. Despite the satisfactory response rates, DOR was not remarkable, while it was associated with significant hematologic toxicity and severe opportunistic infections. Mogamulizumab is a humanized defucosylated monoclonal antibody that targets the chemokine receptor CCR4. CCR4 is highly expressed in Adult T-cell Leukaemia/Lymphoma (ATLL). In this entity it seems to have an important role in contrast to other PTCL, where it is selectively expressed (mainly in AITL). Its mechanism of action is killing tumor cells that are CCR4 positive but it is also directed against regulatory T cells (Tregs) expressing CCR4. As it is known, Tregs create a microenvironment that enablestumor immune evasion. Although data arising from Japanese studies were promising [92], they were not reproduced in a clinical study that was conducted in Europe involving 38 patients with PTCL. In this study ORR was low (11%) and PFS extremely short [93]. Zanolimumab is an anti-CD4 antibody that has been applied in patients with CD4+ PTCL with limited efficacy [87].

4.6. Proteasome inhibitors/ immunodulatory agents

Activation of NF-kB pathway is as key patho genetic mechanism in ALK-sALCL, while it appears to be involved in the subsets of AITL and PTCL-NOS, especially in cases with TBX21 expression [94]. Bortezomibinhibits NF-kB activity and its efficacy is investigated in combination with other agents, such as gemcitabine and panobinostat (HIDAC inhibitor administered orally), with satisfactory results [81]. Lenalidomide, an immunomodulatory agent with anti neo plastic and anti angiogenic properties has also been tested in R/R PTCL with responses ranging from 22 to 30%. These responses are mainly partial with short duration [81,95-97].However in AITL, where the microenvironment plays a special pathogenetic role, lenalidomide is theoretically expected to be active. Based on this theory, there is a current phase II study investigating the efficacy of CHOP/lenalidomide combination in front-line therapy for patients older than 60 years with AITL. The results so far reported are quite satisfactory (ORR: 54%, CR: 46%) [98].

4.7. Kinase inhibitors

Progress in understanding the biology of PTCL, though extremely slow compared to B-celllymphoproliferative disorders has identified unique biological subsets. Several recently discovered genetic alterations involving the T-cell receptor signalling pathway may provide individualized treatment approach with the appropriate kinase inhibitors [99,100].ALK+ sALCL is an example, in which ALK kinase is over expressed as a result of t(2;5)(p23;q35) rearrangement leading to the chimeric gene NPM/ALK. Moreover, 20%of PTCL-NOS are characterized by ITK/Syk rearrangement that results in Syk pathway activation, while PDGFR pathway activation is also present in a subset of PTCL-NOS. Within the entity of ALK- sALCL, a quarter of the cases display aberrant ERBB expression, possibly targetable by the pan-HER inhibitor neratinib [101], while in other cases, genetic aberrations that lead to constitutive activation of STAT3,offer a potential therapeutic target with JAK/STAT3 inhibitors [102]. Crizotinib is an ALK kinase inhibitor. It has impressive efficacy in ALK+ sALCL patients, yielding CR in 9/9 patients. In four of them, DOR was notably long (> 21 to > 41 months) [103]. Alisertib is an Aurora A kinase (AAK) inhibitor. This kinase is necessary for the modulation of the mitotic spindle and regulates the transition from G2 to M phase of the cell cycle. It is over expressed in various malignancies, particularly lymphomas characterized by rapidly proliferating cells, including PTCL. Preliminary data from two phase II studies showed ORR30-50%. On that basis, a randomized phase III study (NCT01482962) was conducted for patients with R/R PTCL comparing the efficacy and safety of alisertib to the investigator's choice including plaratrexate, romidepsin and gemcitabine. However, this study closed

prematurely, as at first interim analysis it became clear that it was not possible to achieve the primary endpoint of the study, namely the superiority of Alisertib regarding PFS [104,105]. Other kinase inhibitors that are investigated in PTCL are Duvelisib, Sorafenib and Masitinib [81,106].

4.8. Immune checkpoint inhibitors

The inhibition of programmed death-1 pathway (PD-1) and its ligands (PD-L1 and PD-L2) has revolutionized treatment in certain malignancies, including Hodgkin Lymphoma. Its main mechanism of action relies on the activation of antitumor T-cell response. There is evidence that Nivolumab – a fully human anti-PD1 monoclonal antibody – shows some activity in PTCL: In a phase 1 study 2/5 patients with PTCL, responded with a PR with DOR of 11 and 79+ weeks, respectively [107]. Whether biomarkers, such as aberrations of PD-L1 and PD-L2 loci correlate with response, remains to be proven. The combination of nivolumab and ipilimumab (anti-CTLA-4 antibody) is being currently investigated [108]. Further clinical data is needed in order to explore the activity of immune checkpoint inhibitors in PTCL and define the subgroup of patients who may benefit from this immunologic manipulation.

Table 4: Retrospective studies about allo-SCT in nodal PTCL.

Authors	Corradini et al. [43]	Feyler et al. [44]	LeGouill et al. [45]	Kyriakou et al. [46]	Dodero et al. [47]
Patients	17	18	77	45	52
Median age (years)	41	28	36	48	
Histologic subtypes (%)	PTCL-NOS: 53 ALCL: 24 AITL: 24	PTCL-NOS:39 ALCL:17	PTCL-NOS: 35 ALCL: 35 AITL: 16	AITL: 100	PTCL-NOS: 44 ALCL: 21
					AITL: 17
Previous ASCT (%)	47	11	25	24	52
Conditioning	Thiotepa/Cy/Flu	Various	RIC: 74%	RIC: 56%	Thiotepa/Cy/Flu
Chemo refractory (%)	12	NR	30	40	25
PFS/EFS (%)	3-year: 64	3-year: 33	5-year: 53 Chemo's: 64 ChemoR: 27	3-year: 54 Chemo's: 66 ChemoR: 33	5-year: 40 ChemoS:51
					ChemoR: 8
OS (%)	3-year: 81	3-year: 39	5-year: 57	3-year: 64	5-year: 50
TRM (%)	2-year: 6	3-year: 39	5-year: 34	1-year: 25	5-year: 12
Median follow-up (months)	28	37	43	29	67

Allo-SCT: Allogeneic Stem Cell Transplantation, PTCL: Peripheral T-cell Lymphomas, ALCL: anaplastic large cell lymphoma, PTCL-NOS: PTCL not otherwise specified, AITL: angioimmunoblastic T-cell lymphoma,ASCT: Autologous Stem Cell Transplantation, OS: Overall Survival, PFS: Progression Free Survival, EFS: Event Free Survival, TRM: Transplant-Related Mortality, Thiotepa/Cy/Flu: combination of thiotepa, cyclophosphamide and Fludarabine, RIC: Reduced Intensity Conditioning, NR: not reported, Chemo's: chemo sensitive, ChemoR: chemoresistant.

Table 5: Novel agents in treatment of PTCL.

Agent	Rationale	Author	Patients	ORR/CR (%)	DoR (months)	PFS (months)	OS (months)
Pralatrexate	Purine/pyrimidine	O'Connor et al. [56]	111	29/11	10.1	3.5	14.5
(Inhibits DHFR)	synthesis inhibition		PTCL-NOS: 59	32			
			AITL: 13	8			
			sALCL: 17	35			
Romidepsin		Piekarz et al. [81]41	47	38/18	9	-	-
(class I HiDAC inhibitor 1, 2, and 3)			PTCL-NOS: 27	41			
			AITL: 7	17			
			ALCL: 4	100			

	Epigenetic deregulation in T-cell lymphomas	Coiffier et al. [61]	130	25/15	28	4	11.3
	Over expression of HIDACs in T-cell lymphomas		PTCL-NOS: 69	29/14			
			AITL: 27	30/19			
			ALK-sALCL: 21	24/19			
Belinostat		O'Connor et al. [65]	120	26/11	13.6	1.6	7.9
(Pan-HiDAC inhibitor)			PTCL-NOS: 77	23			
			AITL: 22	46			
			sALCL: 15	13			
Azacytidine	TET-2 mutations in AITL	Delarue et al. [68]	19	53/26	-	-	-
(hypomethylating agent)			AITL: 12	75/42			
			Other PTCL: 7	15/0			
Brentuximab Vedotin	sALCL express CD30	Pro et al. [69-71]	58 sALCL	86/57	12.6	20	4 years: 64%
(anti-CD30 MoAb + MMAE)			ALK+:16				
			ALK-: 42				
	Some PTCL/AITL express CD30	Horwitz et al. [76]	35	41/24			-
			PTCL-NOS: 22	33/14	7.6	1.6	
			AITL: 13	54/38	5.5	6.7	
Alemtuzu-mab	Some PTCL express-CD52	Enblad et al. [82]	14	36/14	6	-	-
(anti-CD52 MoAb)			PTCL-NOS: 10				
			AITL: 2				
Bortezomib (proteasome inhibitor)	NFkappa B activation in PTCL subsets	Goh et al. [81]	25	43/22	-	-	-
+ Panobinostat (HiDAC inhibitor)	HiDAC expression		PTCL-NOS:11				
			AITL: 8				
			sALCL: 3				
Bortezomib + gemcitabine	NFkappa B activation in PTCL subsets	Evens et al. [81]	16	36/27	-	-	-
			PTCL-NOS: 12				
			AITL: 1				
Denileukin Diftitox	CD25 expression (IL-2 receptor) in some PTCL	Dang et al. [79]	27	48/22	-	6	-
(chimeric protein:							
Diphtheria toxin + IL-2)							
Lenalido-mide	antineoplastic, anti-angiogenic, immunodulatory action, improve of T/NK cells action	Dueck et al. [81]	23	30/0	-	3.1	7.9
(immune-modulatory agent)			PTCL-NOS: 10				
			AITL: 7				
			sALCL: 5				
		Zinzani et al. [81]	10	30/30	19-Nov	-	-
		Morsch-hauser et al. [81]	54	22/11	3.6	2.5	-
			PTCL-NOS: 20				
			AITL: 26	31/15			
			sALCL: 3				
		Toumi-shey et al. [81]	39	26/8	5	4	12
			PTCL-NOS: 14	43/14			
			AITL: 9	33/11			
			sALCL: 10	Oct-00			

Mogamulizu-mab	CCR4 expression by neoplastic T cells and by Tregs	Ogura et al. [81]	37	35/14	-	3	-
(anti-CCR4 MoAb)		Zinzani et al. [81]	38	11	2.9	2.1	
Crizotinib	ALK expression by	Gamba-corti Passerini et al. [103]	9 ALK+ sALCL	100/100		2-years: 64%	2-years: 73%
(ALK inhibitor)	ALK+ sALCL						
Sorafenib	PTCLs express PDGFR, VEGF	Gibson et al. [106]	3	3-Feb	-	-	-
Multikinase Inhibitor (BRAF, PDGFR, VEGF)							
Duvelisib	Inhibits downstream of kinase Syk	Horwitz et al. [81]	16	47/13	-	-	36.4weeks
(PI3Kγ/δ inhibitor)							
Alisertib	PTCLs express AAK	Friedberg et al. [104]	8	50/38	250days	-	1-year: 75%
(Aurora A Kinase, AAK, Inhibitor)		Barr et al. [105]	37	30/7	3	-	-
			PTCL-NOS: 13	31/8			
			AITL: 9	33/0			
			sALCL: 2	50/0			
Nivolumab	Inhibits PD-1 pathway	Lesokhin et al. [107]	PTCL: 5	40/0	-	14 weeks	-
(Anti PD-1 MoAb)							

5. Conclusion

Despite a plethora of new therapeutic agents, the natural history and prognosis of PTCL has not improved significantly. The only exception is BV that may have changed the natural history of sALCL, ALK- in particular. A recent meta-analysis investigating the efficacy and safety of various treatments in R/R PTCL identified BV, gemcitabine and ICE combination chemotherapy as rather efficacious and safe among various salvage regimens [109]. Only the understanding of the biological heterogeneity of these entities will enable their successful treatment. Recently, new biological subcategories have been recognized, involving several intracellular signalling pathways that may enable individualized treatment approaches in the future. Until then, combination strategies are being investigated, such as the combination of BV with CHOP in front-line treatment of CD30+ PTCL. Patients with PTCL should be enrolled in multicenter studies in order to draw right conclusions about the efficacy of currently available treatment strategies.

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