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Special Article - T-Cell Lymphoma

Treatment Options of Mature, Nodal T-Cell Lymphomas

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Abstract

T-cell lymphomas represent only 10-15% of non-Hodgkin lymphomas. T cell lymphomas are more agressive, heterogenous diseases and have worse prognosis than B cell lymphomas. A number of new drugs are tested and approved in the therapy of peripherial T cell lymphomas, which hopefully will increase survival. CHOP and CHOP-like protocol are recommended for the first-line treatment, but it is efficacy alone only in ALK+ anaplastic large cell lymphoma. Guidelines recommend front-line autologous hematopoetic stem cell transplantation in the other most frequent subtypes. A number of new drugs are tested and approved in the therapy of peripherial T cell lymphomas, eg. romidepsin, pralatrexate, belinostat, brentuximab vedotin etc., which hopefully will increase survival.

Keywords: T cell lymphoma; Treatment; New drugs

Abbrevations

AE: Adverse Event; AHSCT: Autologous Hemopoetic Stem Cell Transplantation; AITL: Angioimmunoblastic T Cell Lymphoma; ALCL: Anaplastic Large Cell Lymphoma; ALK: Anaplastic Lymphoma Kinase; CHOP: Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; CHOEP: CHOP+etoposide; CR: Complete Remission; EFS: Event-Free Survival; FDA: Food and Drug Administration; FFS: Failure-Free Survival; HDAC: Histone Deacetylase; NCCN: National Comprehensive Cancer Network; NHL: Non-Hodgkin Lymphoma; OS: Overall Survival; PFS: Progression-Free Survival; PTCL-NOS: Peripherial T-Cell Lymphoma Not Otherwise Specified; TCL: T Cell Lymphoma; WHO: World Health Organization

Introduction

Non-Hodgkin lymphomas (NHLs) originate from T lymphocytes and NK cells in 10-15% of cases, while T-cell lymphomas (TCL) represent approximately 25% of NHLs in Asian countries [1]. There are four main groups of T cell lymphomas in the WHO classification: nodal, extranodal, cutan and leukemic group. New provosional entities of T cell lymphomas are introduced in the new WHO 2016 classification, these changes mostly based on the result of genomic studies [2]. Three subtypes are the most frequent in nodal T cell lymphoma group: peripherial T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and systemic anaplastic large cell lymphoma (ALCL), which may be positive or negative for anaplastic lymphoma kinase (ALK) [2]. T cell lymphomas are more agressive, heterogenous diseases and have worse prognosis than B cell lymphomas. Usually patients have advanced stage disease and extranodal involvement at the time of diagnosis. The minority of patients reach durable remissions or cure after first-line treatment. Treatment of TCLs is unmet medical need nowadays. A number of new drugs are tested and approved in the therapy of PTCLs, which hopefully will increase survival.

Current first-line treatment options

Majority of PTCLs, except for ALK+ ALCL, has bad prognosis. The 5-year overall survival (OS) for ALK+ ALCL, ALK-ALCL, PTCL-NOS and AITL was 70%, 49%, 32% and 32% and the 5-year failure-free survival (FFS) was 60%, 36%, 20% and 18% [3]. The frontline treatment in the most frequent PTCL types is combination chemotherapy, usually anthracycline-based regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), or CHOP+etoposide (CHOEP) with autologous hemopoetic stem cell transplantation (AHSCT) given as consolidation for high risk, selected patients (except ALK+ ALCL) [4,5].

CHOP is the generally recommended and used protocol, but it has moderate efficacy. A retrospective analysis showed 5-year OS was only 37% in 2912 patients, who received CHOP or CHOP-like chemotherapy [6]. The only exception was ALK+ and ALK - ALCL, which has better survival, overall response rate (ORR) >75% and 5-year OS >60% [7]. PTCL-NOS patients who received anthracycline in the initial treatment has no survival benefit than patients who didn't receive it [3].

There were a lot of trials to improve efficacy of the therapy. Some studies used combination therapy eg. CHOP plus etopozid or alemtuzumab, or another chemotherapy eg. ACVBP, VIP-rABDV, alemtuzumab, denileukin diftitox [8]. VIP/ABVD (etoposide/ ifosfamide/ cisplatin–doxorubicin/ bleomycin/ vinblastine/ dacarbazine), CHOP/ESHAP did not improve the outcome [9-11]. Hyper-CVAD/MA (hyper-fractionated cyclophosphamide/ doxorubicin/ vincristine/ dexamethasone alternating with methotrexate/ cytarabine) showed higher ORR and progression-free survival (PFS), but not higher OS, than CHOP [12] in a retrospective study, but this regimen associated with greater toxicity.

The German High-Grade Lymphoma Study Group added etoposide to CHOP (CHOEP) [13]. ORR was 82% and complete remission) CR was 63%. Schmitz, et al. reported that CHOEP treatment is more effective than CHOP in young patients' group, but this treatment was no significantly better in >60 years old patients and it was too toxic in this group [13].

The difference in event-free survival (EFS) for younger patients and ALK+ ALCL treated with CHOP or CHOEP was significant (3-year EFS for CHOEP patients 91.2% vs. 57.1% for patients treated

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Table 1: New first line treament options.

First line treatment	ORR	CR	grade 3/4 toxicities	comment
CHOEP [13]	82%	63%		
CHOP+romidepsin [22]	69%	51%	neutropenia 89%	
romidepsin-CHOP [54]	78%	66%		
Brentuximab vedotin-CHP [47]	100%	88%	febrile neutropenia 31%	only CD30+PTCL
bortezomib-CHOP [50]	76%	65%	neutropenia 41%	
everolimus-CHOP [55]	90%	57%	neutropenia 80%	all AITL were in CR
alemtuzumab-CHOP [57]	68%	37%	neutropenia 70%	only CD52+PTCL
pralatrexate-CEOP [58]	70%	52%	anaemia 27 %	

(ORR: overall response rate, CR: complete response)

Table 2: New salvage treament options.

Salvage treatment	ORR	CR	grade 3/4 toxicities	comment
pralatrexate [20]	29%	11%	thrombocytopenia 33%	AITL had fewer response
romidepsin [21]	38%	18%		
belinostat [23,24]	26%	11%	thrombocytopenia 13%	AITL had ORR 46%
brentuximab vedotin [25]	86%	57%	neutropenia 21%	
bendamustin [28]	50%	28%	neutropenia 30%	
mogamulizumab [29]	50%	31%	lymphopenia 74%	only CCR4+ TCL
mogamulizumab [30]	35%	14%	lymphopenia 73%	only CCR4+ TCL
zanolimumab [31]	24%	10%	lymphopenia 10%	only CD4+ TCL
lenalidomide [32]	30%	0%	thrombocytopenia 42%	
lenalidomide [33]	22%	11%	thrombocytopenia 20%	
alisertib [35]	50%		neutropenia 63%	
crizotinib [37,38]	91%	27%		only ALK+ ALCL
gemcitabin [39]	55%	30%		
bortezomib [40]	67%	13%	neutropenia 13% (only grade3)	
everolimus [44]	44%	6%	anaemia 25%	
duvelisib [45]	47%	13%		
nivolumab [46]	17%			ORR: 40 % in PTCL patients
bortezomib-gemcitabin [51]	36%	27%		
gemcitabin-romidepsin [52]	30%	15%	thrompocytopenia 60%	
gemcitabin-dexamethason-cisplatin [53]	72%	48%	neutropenia 16%	

(ORR: overall response rate, CR: complete response)

with CHOP, p = 0.012), a statistically not significant difference was seen in the remaining patients when ALK+ ALCL was excluded (3-year EFS for CHOEP patients 60.7% vs. 48.3% for patients treated with CHOP, $p = 0.057$) [13].

CHOEP was associated with improved PFS in patients younger than 60 years in a Swedish analyzis also [14].

Autologous transplantation is recommended ALK-ALCL patients in first-line treatment, but not in ALK+ALCL patients [5]. D'Amore, et al. showed 5-year OS 70% and PFS 61% in ALK-ALCL patients who were treated 6 cycles CHOEP followed by AHSCT, if they were in CR/CRu or PR [15]. AHSCT produces better 5-year OS in ALK+ than ALK-patients (82% versus 54%) [16].

Based on these results National Comprehensive Cancer Network (NCCN) guidelines recommend CHOP-21 or CHOEP-21 regimens as the first-line therapy in ALK-positive ALCL and clinical trials and/or frontline AHSCT for first-line therapy in all other subtypes [5].

New therapeutic options

Only half of the TCL patients reached complete remission (CR) after first line treatment and only half of these patients have durable remission [17]. Majority of T-cell lymphoma patients (about 70%) have refractory disease or relapse after the first line treatment [4]. Relapsed/refractory (R/R) PTCL patients' overall survival (OS), who did not undergo AHSCT, 5.5 months only [18].

There is no uniform recommendation to the optimal treatment relapsed and refractory patients. A lot of clinical trials was conducted and these showed various efficacy (Table 1,2). Three new drugs was approved by the FDA in the therapy of R/R PTCL patients, pralatrexate, romidepsin and belinostat.

FDA approved new drugs

Pralatrexate: Pralatrexate, an antimetabolite drug, which selectively enters cells through reduced folate carrier type 1, FDA approved this drug for the treatment of patients with R/R PTCL in 2009. O'Connor, et al. conducted a dose/schedule finding study in R/R lymphomas [19]. ORRs were 10% and 54% in patients with B-cell and T-cell lymphomas respectively. All eight patients who achieved CR had T-cell lymphoma. PROPEL was the first international prospective study of novel therapeutic agents in patients with PTCL [20]. One hundred and nine heavily pretreated PTCL patients recevied the drug, ORR and CR/CRu (CR uncorfirmed) rates were 29% and 11%. Patients with AITL had fewer responses (1 out of 13 patients) than other subtypes. Patients who received only CHOP before pralatrexate, the ORR was 47% and the CR rate was 30%, suggesting that the response rate might be higher if pralatrexate is used earlier, not in heavily pretreated patients. Grade 3/4 adverse events (AEs) were thrombocytopenia (33%), mucositis (22%), neutropenia (22%) and anemia (18%) [20].

Romidepsin: Romidepsin is a new potent class I selective histone deacetylase (HDAC) inhibitor, which was was approved by the FDA in 2011 for the treatment of PTCL in patients who had received ≥ 1 prior therapies. A phase II trial used romidepsin in 47 PTCL patients with various histologic subtypes [21]. Among 45 evaluable patients in this study ORR was 38% and 18% had CR. The most common AEs were nausea (51%), thrombocytopenia (47%), leukopenia (47%), granulocytopenia (45%), fatigue (40%) and anemia (40%) [21]. One hundred and thirty patients were treated with romidepsin in another phase II trial. Most patients had PTCL-NOS ($n=69$), AITL ($n=27$), or ALK-negative ALCL ($n=21$). The ORR was 25% and 15% had CR. The most common grade 3/4 AEs were thrombocytopenia (24%), neutropenia (20%) and infections (19%).

Single-arm, phase Ib/II study used CHOP plus romidepsin as first line treatment in 37 PTCL patients. Among 35 evaluable patients the ORR was 69% and CR was 51%. Three patients had early cardiac events, including two myocardial infarctions and one acute cardiac failure. The most frequent serious AEs were febrile neutropenia 14%, physical health deterioration and lung infection 11%. Grade 3/4 neutropenia were detected in 89% of patients and grade 3/4 thrombocytopenia in 78% [22].

Belinostat: Belinostat is a pan-HDAC inhibitor, which was investigated in R/R PTCL patients in the BELIEF trial. One hundred and twenty-nine patients received belinostat, among the 120 evaluable patients, the ORR was 26%, CR was 11%. ORR was the best, 46% in AITL. The most common grade 3/4 AEs were thrombocytopenia (13%), neutropenia (13%) and anemia (10%) [23,24]. Based on the results of this study FDA approval belinostat in 2014 for treatment of R/R PTCL patients.

Other new therapeutic options

Monotherapy: Brentuximab vedotin: Brentuximab vedotin (BV) is an immunoconjugate of an antitubulin agent and a CD30-specific immunoglobulin G1 monoclonal antibody. Fifty eight ALCL patients were treated with BV in a phase II study, ORR was 86% and CR was 57%. The most common AEs were peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%) and pyrexia (34%). Based on the results of this study, the FDA and European Medicines Agency, in 2011 and 2012, approved the use of BV for patients with systemic ALCL after failure of ≥ 1 multi-agent chemotherapy regimen [25]. Another phase II trial of BV in 35 patients showed ORR of 41% and no correlation between CD30 expression per central review and response was observed [26]. Grade 3/4 adverse events were neutropenia (21%), thrombocytopenia (14%) and peripheral sensory neuropathy (12%) [27].

Bendamustine: Bendamustine is an alkylating agent with antimetabolite effect. In the BENTLY trial, 60 patients with CTCL and PTCL (mainly AITL and PTCL-NOS) were treated with bendamustine**.** The ORR was 50% and CR was 28%. The most frequent grade 3/4 AEs were neutropenia (30%), thrombocytopenia (24%) and infections (20%) [28].

Mogamulizumab: Mogamulizumab is an anti- CC chemokine receptor 4 (CCR4) monoclonal antibody. Mogamulizumab depletes CCR4-positive regulatory T cells and help to enhance antitumor activity. Twenty-seven relapsed agressive CCR4-positive T cell lymphoma patients received mogalizumab in a phase II study. ORR was 50% and CR was 31%. The most common grade 3/4 AEs were lymphopenia (74%), leukocytopenia (30%), thrombocytopenia (19%), neutropenia (19%) and rash (19%) [29]. Another phase II study of mogamulizumab at the same dose in 38 patients, of whom 37 were evaluable with relapsed CCR4-positive PTCL or CTCL, reported an ORR of 35%, including 14% with a CR. The most common grade 3/4 AEs were lymphopenia (73%) and neutropenia (19%) also [30].

Zanolimumab: Zanolimumab is an anti-CD4 monoclonal antibody. Twenty-one R/R CD4+ PTCL patients were treated with zanolimumab ORR was 24% and CR was 10%. Grade 3 AEs were lymphopenia (10%), infusion-related AEs (10%) and arthralgia (5%) [31].

Lenalidomide: Lenalidomide is an immunomodulatory drug which inhibits vascular endothelial growth factor (VEGF), activation of natural killer cells and T lymphocytes and modulates various cytokines such as tumor necrosis factor-α, interleukin-12 and interferon-γ. A phase II study used lenalidomid in 24 patients. Among the 23 evaluable patients, ORR was 30%, but there are no patients in CR. The most common grade 3/4 AEs were thrombocytopenia (42%), neutropenia (21%), dyspnea (17%), febrile neutropenia (17%), pain (17%) and pneumonitis (17%) [32]. EXPECT was an phase II study which included 54 patients with R/R PTCL. ORR was 22%, CR/CRu was 11%. Most common grade 3/4 AEs were thrombocytopenia (20%), gastrointestinal disorders (17%), neutropenia (15%) and infections (15%) [33].

Alisertib: Aurora A kinase (AAK) is a mitotic kinase which is upregulated in PTCL [34]. Alisertib is an oral selective AAK inhibitor, a phase II trial evaluated its efficacy in refractory T-cell and B-cell lymphomas. ORR was 50% in eight PTCL patients. Grade 3/4 AEs were neutropenia 63%, leukopenia 54%, anemia 35%, thrombocytopenia 33% and stomatitis 15% [35]. Thirty-seven R/R PTCL patients were treated in another phase II intergroup trial (SWOG 1108). Among ORR was 30% Grade 3/4 AEs were neutropenia (32%), anemia (30%), thrombocytopenia (24%), febrile neutropenia (14%), mucositis (11%) and rash (5%). Based on these results, a randomized phase III trial of

alisertib versus the investigator's choice (pralatrexate or gemcitabin monotherapy) was designed for patients with relapsed PTCL, but study was closed earlier due to alisertib was not more effective than other treatments [17,36].

Crizotinib: Crizotinib is an oral small-molecule tyrosine kinase inhibitor of ALK, which has been FDA approved for the treatment of lung cancer. Eleven refractory ALK+ lymphoma patients (9 ALCL) received crizotinib ORR was 91%, CR was 27%. There were no grade 3/4 toxicity [37,38]. A clinical trial is ongoing in ALK+ ALCL patients with use of crizotinib.

Gemcitabin: Gemcitabin is a nucleoside analog, which inhibits DNA replication and repair. Other nucleoside analogs are pentostatin, cladribine, fludarabine, clofarabine, forodesine and nelarabine. These agents are cytotoxic to both proliferating and non-proliferating cells. Gemcitabine, cladribine and fludarabine have shown efficacy in PTCL and gemcitabine is the most effective in PTCL. NCCN guidelines recommends as second-line therapy for patients with relapsed PTCL [5]. Twenty R/R PTCL-NOS patients were treated with gemcitabine [39]. ORR was 55% and CR was 30%. There was no grade 3/4 hematological toxicity.

Bortezomib: Bortezomib is a proteasome inhibitor. Fifteen relapsed CTCL or PTCL patients got in a phase II trial. ORR was 67% and CR was 13%. The most common grade 3 toxicities were neutropenia (13%), thrombocytopenia (13%) and sensory neuropathy (13%) and there was no grade 4 toxicity [40]. The NCCN has recommended bortezomib as a second-line therapy for patients without intention to proceed to transplantation [5].

AG-221: Isocitrate dehydrogenase 2 (IDH2) mutations have been identified in solid tumors and hematologic malignancies eg. glioblastoma, acute myeloid leukemia and myelodyplastic syndromes. AML and MDS patients reached 56% ORR with IDH2 inhibitor (AG-221) in a phase I study [41]. IDH2 mutations are frequent in AITL (20-45%) so IDH2 inhibitor can be effective in this lymphoma type [42,43].

Everolimus: The mTOR pathway is responsible for TCL proliferation. Everolimus is a mTORC1 inhibitor. Sixteen relapsed TCL were treated with everolimus in a phase II study. The ORR was 44% and CR was 6%. Grade 3/4 AEs were anaemia (25%), leukopenia (19%) and thrombocytopenia 13%) [44].

Duvelisib: Duvelisib (IPI-145) is an oral phosphatidilinozitol 3-kinase inhibitor (PI3K). Sixteen PTCL patients received duvelisib. ORR was 47% and CR was 13% [45].

Nivolumab: Programmed death-1 (PD-1) immune checkpoint pathway help tumour cells to avoid immune surveillance. Nivolumab is a PD-1 inhibitor, which is approved by FDA in the treatment of Hodgkin lymphoma. The activity of nivolumab in other lymphoid malignancies also has been presented [46]. Responses also were seen in 23 patients with TCL, with superior response seen in patients with PTCL. The ORR for patients with TCL was 17%, there was no CR. The ORR in patients with PTCL was 40% and was 15% in those with cutaneous T cell lymphoma [46].

New combination therapy: Brentuximab vedotin-CHP: BV and CHP combination therapy was examined in a phase I open-label study as frontline treatment in patients with CD30-positive PTCL. Twenty-six patients were treated, all of them achieved an objective response and CR was 88%. Grade 3/4 AEs were febrile neutropenia (31%), neutropenia (23%), anemia (15%) and pulmonary embolism (12%) [47]. A randomized phase III trial is ongoing, comparing BV and CHP combination with CHOP alone.

Alemtuzumab-CHO(E)P: Alemtuzumab is an anti-CD52 monoclonal antibody that causes depletion of CD4 and CD8 T cells as well as B cells. Alemtuzumab combined with CHO(E)P was investigated 29 patients as consolidation therapy in a phase II trial, CR rate was 58.5%. Grade 3/4 toxicities were infections (14%) [48]. Another phase II study investigated combination of alemtuzumab, fludarabine, cyclophosphamide and doxorubicin in 27 PTCL patients' first line treatment and 11 R/R PTCL patients. ORR was 61%, with a CR of 39%. The most frequent grade 3/4 toxicities were leukopenia (95%) and thrombocytopenia (58%). Cytomegalovirus (CMV) reactivation was detected in 12 patients, but only two had CMV disease. Treatment-related deaths occurred in six newly diagnosed and one R/R patient [49]. Alemtuzumab-based therapy was active in PTCL but was associated with significant toxicity.

Bortezomib-CHOP: Forty six patients were treated with bortezomib plus CHOP as firstline treatment. ORR was 76% and CR was 65%. Outcome was similar to CHOP alone. Grade 3/4 neutropenia was in 41% of patients, febrile neutropenia in 30% and thrombocytopenia in 11% [50].

Bortezomib-gemcitabin: Bortezomib with gemcitabin was used in 16 R/R PTCL patients in a phase I/II ORR was 36% and CR was 27% [51].

Gemcitabin-romidepsin: A phase II trial was conducted in R/R PTCL. Twenty patients were treated with combination of gemcitabine plus romidepsin (GEMRO regimen). The ORR was 30%, 3 patients had CR. Two-year OS was 50% and PFS 11.2%. Sixty percent of the patients had grade ≥3 thrombocytopenia, half of the patients had neutropenia. The majority of non-hematological toxicities were mild and transient. There was no treatment-related death or toxicity which led to treatment interruption [52].

Gemcitabin-dexamethason-cisplatin: CISL trial investigated GDP (gemcitabin-dexamethason-cisplatin) protocoll in 25 R/R PTCL patients. ORR was 72% and CR was 48%. Grade 3/4 neutropenia (16%) and thrombocytopenia (13%) was occurred [53].

Romidepsin-CHOP: Romidepsin plus CHOP was investigated in a phase Ib/II study in first line treatment of 14 PTCL patients. ORR was 78%, CR was 66% [54].

Everolimus-CHOP: A phase II study investigated the efficacy of everolimus plus CHOP therapy for first-line treatment in PTCL. Thirty patients were treated, ORR was 90%, CR was 57%. The CR rate was different among subtypes, all AITL patients had CR whereas PTCL-NOS and ALK-negative ALCL patients showed 63% and 29% CR. Eighty percent of patients suffered grade 3/4 neutropenia and 60% of patients had grade 3/4 thrombocytopenia [55].

Pirarubicin-COP: Pirarubicin is a derivative of doxorubicin, which is less cardiotoxici than the doxorubicin. A retrospective study analysed 56 patients with PTCL-NOS who had received pirarubicin

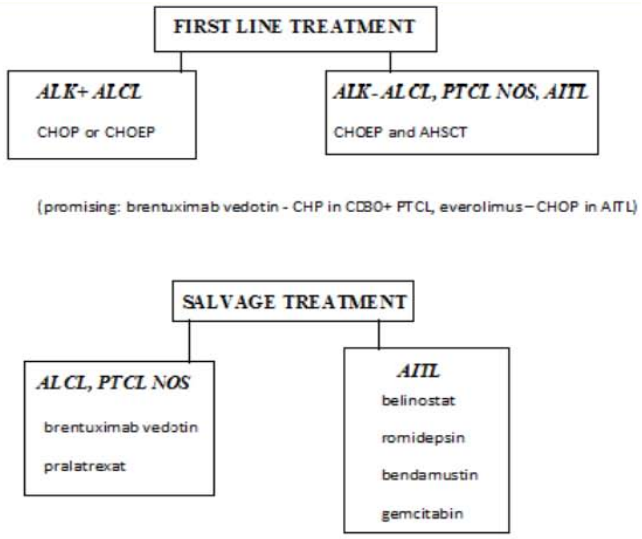

Figure 1: Treatment options (other than clinical trials) in mature, nodal T cell lymphoma.

plus COP or CHOP treatment. Twenty-nine patients received pirarubicin and COP and 27 received CHOP. CR was 52% in both groups and there were no significant differences in 3-year OS and PFS rates. Pirarubicin and COP led significantly better prognosis in low risk patients [56].

Alemtuzumab-CHOP: Phase I trial was conducted in 20 CD52-positive PTCL patients. ORR and CR were 68% and 37%. Grade 3/4 neutropenia were in 70% of the patients and thrombocytopenia 20% [57].

Pralatrexate-CEOP: First-line cyclophosphamide, etoposide, vincristine and prednisone (CEOP) alternated with pralatrexate treatment was used in a phase 2 study. Thirty-three PTCL patients were treated with this protocol. ORR was 70% and 52% of the patients had CR. The 2-year OS and PFS were 60% and 39%, so this new combination did not improve outcomes compared to historical data using CHOP. The most frequent grade 3/4 AEs were anaemia in 27% of patients and febrile neutropenia in 18% of patients [58].

Pixantrone-etoposid-bendamustin: Pixantrone is an analogue of mitoxantrone, but it has fewer cardiotoxic effect. A phase 1/2 study (pixantrone, etoposide and bendamustin) is ongoing in B- and T-cell lymphoma patients.

NCCN recommends in second-line therapy as single-agent treatment: clinical trials, belinostat, romidepsin, pralatrexat and brentuximab vedotin in CD30+ PTCL, or combination therapy (eg. DHAP, ESHAP, ICE). Other alternative regimens (eg. bendamustin, gemcitabin, lenalidomid) can also be used (Figure 1)[5].

Conclusion

TCLs are aggressive, heterogenous, rare lymphoma types. There are a lot of subtypes in the WHO 2016 classification, but relatively few patients in Europe and USA, so the diagnosis is usually difficult. CHO(E)P chemotherapy is usually recommended for the first-line treatment, but it is not effective in majority of PTCLs (except ALK+ALCL). Frontline AHSCT is suggested for all other subtypes. Remission can be reached mostly, if patients undergo AHSCT in CR/CRu, but it is difficult due to the inadequate firstline chemotherapy possibilities, so guidelines recommend patient's treatment in clinical trials. Use of PET/CT is also suggested in the staging and in response assessment. AHSCT can be more successfull if PET/CT show CR after chemotherapy. Prognosis is very poor in relapsed patients. Several drugs were tested in the treatment of TCLs in last years, but roaring succes was not reached. Long-term remission is the basis of the cure, so better efficiency therapy must be found.

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