

SIE-SIES-GITMO Guidelines for the management of adult peripheral T- and NK-cell lymphomas, excluding mature T-cell leukaemias

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Background: In order to promote widespread adoption of appropriate clinical practice, the Italian Society of Hematology (SIE), and the affiliate societies SIES (Italian Society of Experimental Hematology) and GITMO (Italian Group for Bone Marrow Transplantation) established to produce guidelines in the most relevant hematological areas. In this article, we report the recommendations for management of T/NK-cell lymphomas, excluding mature T-cell leukaemias.

Design: By using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) system, we produced evidence-based recommendations for the key clinical questions that needed to be addressed by a critical appraisal of evidence. The consensus methodology was applied to evidence-orphan issues.

Results: Six courses of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHOEP) chemotherapy were recommended for first-line therapy of patients with nodal, intestinal or hepatosplenic T-cell lymphomas (evidence: low; recommendation: do, weak). Except for ALK+ anaplastic large-cell lymphoma and elderly unfit patients, consolidation with high-dose chemotherapy was recommended (evidence: low; recommendation: do, weak). 50 Gy radiotherapy was the recommended first-line therapy for localized extranodal T/NK-cell lymphoma nasal type (evidence: low; recommendation: do, strong), while L-asparaginase-containing chemotherapy regimens were recommended for patients with systemic disease (evidence: very low; recommendation: do, strong).

Conclusion: In adult T/NK-cell lymphomas, GRADE methodology was applicable to a limited number of key therapeutic issues. For the remaining key issues, due to lack of appraisable evidence, recommendations was based on consensus methodology.

Key words: T/NK-cell lymphoma, clinical practice guidelines, hematopoietic stem cell transplantation

introduction

The Italian Society of Hematology (SIE), and the affiliate societies SIES (Società Italiana di Ematologia Sperimentale) and GITMO (Gruppo Italiano Trapianto Midollo Osseo) have established to produce guidelines for the most relevant hematological issues. In this article, we report the results of the project of practice guidelines for the management of adult peripheral T- and NK-cell lymphomas (PTCLs).

PTCLs account for about 12% of lymphoid malignancies [1]. PTCLs are rare disorders with a dismal prognosis and for which few treatment options are available [2]. The WHO classification has divided this group of disorders into those with predominantly leukemic from those with nodal, extranodal or cutaneous presentation [1]. The present guidelines address specifically to the management of non-leukemic adult PTCLs (Table 1).

methods

guidelines development process

The Advisory Council (AC), composed of three members with expertise in clinical epidemiology, haematology and critical

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Table 1. Peripheral T- and NK cell neoplasms (excluding mature T-cell leukaemias)

| |
|--|
| Nodal peripheral T-cell lymphomas (PTCL) |
| Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) |
| Angio-immunoblastic T-cell lymphoma (AITCL) |
| Anaplastic large-cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK) positive |
| Anaplastic large-cell lymphoma (ALCL), ALK negative (provisional) |
| Extranodal PTCL |
| Extranodal NK-/T-cell lymphoma, nasal type |
| Enteropathy-associated T-cell lymphoma (EATL) |
| Hepatosplenic T-cell lymphoma (HSTL) |
| Subcutaneous panniculitis-like T-cell lymphoma ($\alpha\beta$ only) (SPTCL) |
| Cutaneous T-cell lymphoma (CTCL) |
| Mycosis fungoides (MF) |
| Sezary syndrome |
| Primary cutaneous CD30+ T-cell lymphoproliferative disease |
| Primary cutaneous PTCLs |

WHO classification 2008 [1].

appraisal, oversaw the process. An Expert Panel (EP) was selected according to the conceptual framework elements of the NIH Consensus Development Program [3].

producing and grading evidence-based recommendations

The AC selected the clinical questions that needed to be addressed by a critical appraisal of evidence. The EP chose the critical outcomes for each clinical query. Literature search was limited to publications edited after 2005. The search included proceedings 2010 through 2012 of the American Society of Hematology, the European Hematology Association and the 11th International Conference on Malignant Lymphoma. According to GRADE methodology [4], the AC prepared ‘evidence tables’ and ‘quality-of-evidence tables’ for each critical appraisal. The EP drafted recommendations based on the benefit to risk profile of each compared intervention. Definite agreement of the recommendations and their strength (weak or strong) was made through subsequent face-to-face meetings. Even though the recommendations were issued on the basis of systematic review of literature published up to December 2012, analysis of data published since that date up to September 2013 was carried out before publication of the present paper.

producing consensus-based recommendations

The consensus methodology was applied by the EP for all the issues not addressable by a critical appraisal. During three consecutive consensus conferences, the issues were analysed and discussed according to the nominal group technique, as previously described [5].

results

issue 1: diagnostic requirements (consensus-based recommendations)

The characterization of pathological subtypes of PTCL is mandatory in order to optimize prognosis and therapy. The antibodies raised against T-cell receptor (TCR) β and γ chains, are useful for the differential diagnosis between $\alpha\beta$ and $\gamma\delta$ PTCLs. CD30 plays a basic role in the recognition of anaplastic large-cell lymphomas (ALCLs), CD30+ cutaneous lymphoproliferative disorder (CTLPD) and the rare CD30+ PTCLs–NOS. ALCLs are further distinguished in ALK+ and ALK– depending on the occurrence or not of the $t(2;5)$ translocation and variants. ALK– ALCL is morphologically and phenotypically indistinguishable from the ALK+ form; however, the distinction between the two entities is of practical relevance, since the former behaves much better than the latter [6]. CD16, CD56 and CD57 in variable combinations and often in association with cytotoxic markers assist in diagnosing NK-cutaneous lymphoma, hepatosplenic T-cell lymphoma (HSTL), enteropathy-associated T-cell lymphoma (EATL) type II and enteropathy-associated NK-cell lymphoma (ENKTCL/NT).

Some other markers specifically have a prognostic values, such as Ki-67 rate. Also the T-cell or NK-cell lymphomas showing positivity of neoplastic cells for Epstein-Barr virus (EBV) are characterized by a very aggressive behaviour. A variable proportion of PTCLs–NOS, in fact, show positivity of neoplastic cells for EBV. In 23 patients with PTCL nasal type who underwent bone marrow (BM) biopsy for EBV, search for EBV, especially by EBER *in situ* hybridization, was positive in 10 [7]. A lower survival rate was seen in patients with BM positive for EBER, suggesting that EBER positivity in BM is the major determinant of a poor prognosis. Some markers, such as $t(6;7)$ and TP63 abnormalities, specifically allow to stratify the prognosis of ALK– ALCL [8, 9].

Recommendations

The pathological diagnosis of NK/T-cell lymphomas requires the integration of clinical data, morphology, immunohistochemistry, flow cytometry, cytogenetics and molecular biology. This complex multi-criteria diagnostic pathway translates into a high risk of misdiagnosis. The referral of tissue specimens to national reference centres with high expertise in the field is highly recommended.

The first diagnostic target is the assessment of the neoplastic nature of a given T-cell population. Even though CD5 and CD7 are the most frequently defective markers, the application of a larger panel from CD2 to CD8 antibodies is recommended (Table 2).

In cases with documented T-cell lymphoma, a subtype pathological characterization is mandatory for prognostic and therapeutic reasons. Such characterization is based on immunohistochemical and molecular characterization.

Antibodies against the β and γ chains of the T-cell receptor (TCR) can be usefully applied for the distinction of tumours derived from $\alpha\beta$ and $\gamma\delta$ T-lymphocytes, respectively. The usage of antibodies against the ALK protein is pivotal for the differential diagnosis between ALK+ and ALK– anaplastic large-cell lymphomas (ALCL).

Besides immunohistochemical staining, the detection of clonal rearrangement of the genes encoding for the TCR is pivotal for the

distinction between partial lymph node involvement by peripheral T-cell lymphoma (PTCL) and paracortical T-cell hyperplasia.

Immunohistological markers of aggressiveness are mandatory to better characterize the prognostic classification of these lymphomas. The Ki-67 marking is included in the modified prognostic index for peripheral T-cell lymphoma unspecified (PIT) (prognostic index for PTCL, not otherwise specified) in which BM involvement is substituted by a Ki-67 rate >80%.

The search for EBV is recommended. EBER should be carried out on BM specimens of patients with nasal PTCL to identify the presence of EBER positive cells, which appears to carry a poor prognosis.

issue 2: pre-treatment evaluation and staging requirements (consensus-based recommendations)

The International Prognostic Index (IPI) predicts the outcomes in all PTCL subtypes by including age, serum lactic dehydrogenase (LDH) levels, and performance status [10]. The index was further refined by the adjunct of BM involvement (PIT score) [11] or Ki-67 (modified PIT score) [12]. The recently proposed Glasgow Prognostic score [13], including C-reactive protein and albumin assessment, is potentially useful for a better stratification in low-risk patients, however, still waits for validation. In the NK subset of extranodal disease, high β 2-microglobulin values and EBV-DNA load are all unfavourable prognostic factors; however, the standard stratification is done according to Korean Prognostic Index (KIPI), which also allows to predict CNS involvement [14, 15] (Table 3).

Recommendations

After a diagnosis of PTCL, common clinical evaluations useful for staging and prognostic assessment should include: physical examination and performance status evaluation; complete blood count; biochemistry (liver and kidney function tests, LDH, total serum proteins, protidogram).

Bone marrow trephine biopsy, contrast-enhanced whole-body CT scan, Waldeyer ring examination and ear-nose-throat evaluation should be carried out except for early (I and IIA stages) mycosis fungoides. In nodal PTCL, pre-treatment evaluation should also include: serum immunoglobulin assay and direct anti-globulin test.

In enteropathy-associated T-cell lymphoma (EATL), pre-treatment evaluation should also include: test for coeliac disease and colonoscopy with last ileum loop examination and random biopsies.

¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography scanning is not routinely recommended. However, in patients with nasal-type PTCL, PET is recommended since it was documented to be a valuable modality for staging and treatment planning [16].

In erythrodermic cutaneous T-cell lymphoma (CTCL), T-cell associated antigens (CD2, CD3, CD4, CD7, CD8, CD26) should be evaluated in peripheral blood lymphocytes.

In all forms of PTCL except for CTCL, Ann Arbor staging should be used to define disease extension. In CTCL, the ISCL-EORTC system should instead be used.

IPI prognostic index should be used for nodal PTCL. For PTCL, a specific Korean-IPI (KIPI) prognostic index has been proposed. PIT prognostic index should also be used for PTCL-NOS.

Table 2. List of markers applicable to formalin-fixed, paraffin-embedded tissue sections for the diagnosis of peripheral NK/T-cell lymphomas

| | Markers |
|--------------------------------------|--|
| T cell | CD2, CD 3, CD 4, CD5, CD7, CD8, CD52, β F1, TCR γ |
| Cytotoxic | TIA1, granzyme B, perforin |
| FTH (follicular helper T cell) | CD10, Bcl6, PD1, CXCL13, SAP, ICOS, CCR5 |
| Treg | FoxP3 |
| NK | CD16, CD56, CD57 |
| Activation | CD25, CD30 |
| Proliferation | MIB1/Ki67 |
| B cell | CD20, BSAP/PAX5 |
| EBV | EBER ISH (<i>in situ</i> hybridization), LMP1, EBNA2 |
| Follicular dendritic cells | CD21 |
| Histiocytes and epithelioid elements | CD68/PG-M1 |
| Others | CCR4, ALK, EMA, CD45 |

Table 3. Prognostic index in peripheral T-cell lymphomas

| IPI (all patients) | K-IPI | PIT |
|--|---|--|
| Factors | Factors | Factors |
| 1) Age (≤ 60 versus >60 years) | 1) B symptoms | 1) Age >60 years |
| 2) Serum LDH ($\leq 1 \times$ normal versus $>1 \times$ normal) | 2) Stage ≥ 3 | 2) ECOG PS ≥ 2 |
| 3) Performance status (0 or 1 versus 2–4) | 3) LDH level $>1 \times$ upper normal limit | 3) LDH level more than $1 \times$ normal value |
| 4) Stage (I or II versus III or IV) | 4) Regional lymph nodes (N1–N3, not M1) | 4) BM involvement |
| 5) Extranodal involvement (≤ 1 site versus >1 site) | | |
| Index | Index | Index |
| Low = 0 or 1 | Group 1: no adverse factors | Group 1: no adverse factors |
| Low intermediate = 2 | Group 2: 1 factor | Group 2: 1 factor |
| High intermediate = 3 | Group 3: 2 factors | Group 3: 2 factors |
| High = 4 or 5 | Group 4: 3 or 4 factors | Group 4: 3 or 4 factors |

issue 3: first-line therapy in nodal T-cell lymphoma, intestinal and hepatosplenic T-cell lymphomas (evidence-based recommendations)

The Panel devised the following key questions to be analysed according to GRADE appraisal of evidence.

For patients with nodal, intestinal and hepatosplenic T-cell lymphoma, is there a therapy better than cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in ameliorating complete response (CR) and progression-free survival (PFS) provided that an acceptable toxicity was assured?

According to a meta-analysis of studies in patients with PTCL treated with anthracycline-based regimens, 2-year event-free survival (EFS) of 38% is expected after standard CHOP and 5–10% toxic mortality [17]. Only two regimens proved weak evidence of superiority to CHOP for first-line treatment: etoposide-enhanced CHOP in young or ALK+ patients, and intensified induction with ifosfamide, vepeside and epirubicin plus methotrexate followed by upfront autologous stem cell transplantation (ASCT) in EATL [18]. Four studies, including two randomized trials, compared etoposide containing CHOP versus CHOP [19–22]: no advantage in OS was ever detected. However, amelioration of PFS by 10%–20% in patients aged <60 years and ALK+ was reported [21] versus a higher grade 3–4 toxicity and hospitalization in the elderly [20]. Indirectness and mild inconsistency in the CR and PFS outcomes caused the evidence to be judged of low quality. However, the EP judged that the benefit-to-risk balance in young patients was favourable.

The adjunct of bleomycin to CHOP (ACVBP) was judged to be inferior to CHOP due to a twice as high toxic mortality with ACVBP, especially in elderly patients and in those with a poor performance status, as reported by two phase II studies [23, 24]. Therefore, the EP judged that the survival benefit, i.e. improved EFS and OS, reported in the 60- to 70-year subgroup could not balance the higher toxicity over CHOP, and provided recommendation against ACVBP (evidence very low).

Uncertainty was reported by the EP regarding first-line CHOP14 when compared with CHOP21 [21], since EFS amelioration was documented in both old and young low-risk patients without a relevant increase of toxicity. However, the advantage was not judged clinically relevant and the quality of evidence was low due to inconsistency, imprecision and indirectness of the unique study addressing this comparison. Similarly, no evidence is available supporting a preference for eight versus six CHOP courses.

Evidence regarding the combination of CHOP with alemtuzumab consists of four phase II studies [25–28]. No consistent demonstration of improved survival could be inferred. A variable CHOP14 or CHOP21 and six or eight cycles schedule were applied; therefore, the overall quality of the evidence was judged to be very low due to limitations and imprecision. A NCI trial with low number of patients reported a survival plateau with dose-adapted etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone (EPOCH) and Campath [29]. The EP could not reach a consensus on the benefit-to-risk-ratio of C-CHOP for first-line therapy.

Evidence was insufficient to support any recommendation regarding the adjunct of denileukin diftitox [30] or bortezomib [31] to CHOP, as well as gemcitabine to CHEOP [32].

In summary, the EP agreed that CHOP remains the standard chemotherapy for nodal, intestinal and hepatosplenic T-cell lymphoma. Exception could be etoposide-containing CHOP in young patients and those with ALK+ lymphomas (evidence: low; recommendation: do, weak). The adjunct of bleomycin to CHOP induces a high toxicity not balanced by increased effectiveness (evidence: low; recommendation: do not do, weak).

For young patients (<65 years old) with nodal, intestinal and hepatosplenic T-cell lymphomas is frontline autologous stem cell transplantation (ASCT) better than standard chemotherapy?

We identified eight prospective studies applying consolidation ASCT in at least 15 PTCL patients achieving a first complete

remission [11, 33–40], and some retrospective studies enrolling >50 patients [41–45]. A small randomized study compared different induction regimens [11], while a second one compared chemotherapy (ACVB or NCVB) with versus without consolidation ASCT [38]. With the former, a higher toxicity and lower survival with megaCHOEP when compared with cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHOEP) induction was found. With the latter, higher but not statistically significant survival rates were reported with ASCT consolidation. A non-statistically significant trend was also reported by a retrospective case-control study by GELA [44]. A retrospective study addressed to EATL reporting 26 patients treated with IVE/MTX-ASCT regimen: EFS and OS were significantly better in patients assigned to intensive versus standard anthracycline-based therapy [18]. One retrospective study [45] reported lower relapse rate by the use of TBI.

The EP agreed that in young patients with nodal, intestinal and hepatosplenic T-cell lymphomas, frontline ASCT was better than standard chemotherapy (evidence: very low; recommendation: do, weak). Results cannot be extrapolated to patients aged over 65 years or with ALK+ ALCL.

Recommendations

The enrolment into clinical trials with new and experimental drugs should be highly recommended in patients with PTCL.

In patients aged 65 years or younger, with nodal, intestinal or hepatosplenic T-cell lymphoma, except for ALK + ALCL, six courses of CHOP or CHOEP (induction phase) followed by ASCT (consolidation phase) is the recommended therapy.

For ALK+ ALCL patients with an IPI score < 3, the induction phase with CHOP or CHOEP × 6 courses without the consolidation phase is recommended.

Patients older than 65 years, CHOP or CHOP-like regimens are the first therapeutic options. In patients fit to intensive chemotherapy, the approach used in younger patient can be considered.

issue 4: first-line therapy in extranodal PTCL nasal type (evidence-based recommendations)

For patients with disseminated extranodal PTCL nasal type, is there a first-line chemotherapy better than CHOP, i.e. ameliorating CR and PFS provided that an acceptable toxicity was assured?

Etoposide-based regimens such as EPOCH or etoposide, ifosfamide, cisplatin, dexamethasone did not prove to increase CR or PFS, the critical end points selected by the EP for evidence evaluation [46]. Enhancement of CHOP/CEOP with oral nitrosureas in limited-stage patients provided prolonged PFS in a retrospective study [47], but the data were not confirmed by a randomized phase II study [48]; therefore evidence was not considered conclusive.

A L-asparaginase-based regimen (SMILE) was applied upfront to 38 advanced-stage patients enrolled in a phase II trial: short-term OS was 55% [49] which is promising when compared with historical data [50–52].

On the basis of the reported evidence, the EP agreed that L-asparaginase-containing regimens such as SMILE or Aspa-Met-Dex [53] can obtain better response rates (RRs) and PFS than CHOP (evidence: low; recommendation: do, strong).

However, the toxicity of SMILE is so high that it should not be used without optimal supportive care.

For patients with limited-stage PTCL nasal type is combined chemioradiotherapy (CRT) better than CT or radiotherapy (RT) alone in providing a CR, provided that an acceptable toxicity was assured?

All of the studies allowing comparisons among treatments were retrospective. RT 50 Gy alone achieved 69% PFS in stage I patients [54, 55], which corresponded to a relevant improvement of survival rate (from 15%–27% to 50%–83% at 5 years) when compared with CT alone [56].

RT doses >50 Gy achieved better survival rates at regression analyses [57–61]. Higher doses inevitably increased toxicity [62]; however, grade 3–4 adverse events are usually not reported [63].

RT followed by CT significantly improved RR and survival versus CT alone in three retrospective studies in patients with limited-stage disease [57, 58, 64]. Results from retrospective studies are not consistent with the survival advantage of CRT when compared with RT alone [61, 65, 66]. However, in the largest retrospective cohort [57] and recent studies [67, 68], median survival duration was significantly longer in patients treated with CRT (72 versus 42 months). Patients with CR achieved a survival rate of 80% at 5 years [63]: therefore, CR appears to be a robust intermediate end point in this setting.

In stage I patients, RT achieved better survival rates (90% versus 49% at 5 years) when applied upfront rather than after CT [58], but a recent phase II study confirmed satisfactory survival rates (75% at 5 years) with EPOCH CT followed by involved field radiotherapy [46] in localized nasal extranodal NK lymphoma. Similar data (survival rates >78% at 2–3 years) were reported by two phase I/II studies applying concurrent RT [67–70] and CT with various agents including etoposide, ifosfamide, vincristine, L-asparaginase and platinum. Despite such favourable results, no comparison of schedules including concurrent or subsequent RT was conducted versus CT alone. Moreover, several studies reported high rates of progression during (anthracycline-based) CT not preceded by RT. Therefore, the EP favoured the classic upfront schedule.

On the basis of the above reported evidence, the essential treatment modality in limited-stage NK/T-cell lymphoma nasal type is RT which is significantly more effective than CT (evidence: very low; recommendation: do, weak). It should be used at doses higher than those usually employed in lymphoma, of

50–54 Gy, and it should be given upfront and not after CT. The benefit of adding CT either concurrently or after RT is less proven, particularly in localized disease.

In patients with extranodal PTCL nasal type, does haematopoietic stem cell transplantation (HSCT) prolong PFS or overall survival (OS)?

A few reports analysed high-dose CT in the subset of PTCL nasal type [71]. Retrospective data on allogeneic stem cell transplantation (allo-SCT) in refractory/relapsed patient support its feasibility and potential benefit [72–77].

The Panel agreed on claiming that ASCT carried out in patients with bad prognostic features during complete remission may prolong survival. Allo-SCT can rescue a proportion of patients with chemosensitive relapse (evidence: very low; recommendation: uncertain).

Recommendations

The treatment of PTCL nasal type differs according to the extent of the disease. Patients with localized disease should receive radiotherapy as early as possible at doses of at least 50 Gy to the tumour and adjacent structures

The evidence is not sufficient to routinely support CT concurrently or sequentially to RT.

Patients with systemic disease should receive L-asparaginase-containing regimens. The SMILE protocol proved to produce the best results, although toxicity was not negligible.

The use of autologous HSCT should be considered during first complete remission.

RT should be added to areas of bulky or residual disease.

issue 5: first-line therapy in panniculitis (consensus-based recommendations)

For patients with panniculitis, is chemotherapy better than local radiotherapy, i.e. ameliorating PFS provided that an acceptable toxicity was assured?

Published case series of panniculitis never exceed 20 patients, and they do not distinguish $\alpha\beta$ from $\gamma\delta$ entities [78]. An array of treatments have been successfully applied: pulse steroids [79], bexarotene [80], cyclosporine [81, 82], methotrexate, anthracycline-based chemotherapy [83, 84], romidepsin [85]. RT was judged a reliable therapeutic option for localized disease, mostly

Table 4. Novel agent response data in relapsed T-cell lymphoma

| Regimen (reference) | No. of patients | Response | PFS (months) | OS |
|---|-----------------|-------------------|----------------|---------------------|
| Bendamustine (Damaj et al.) [107] | 38 | ORR, 47%; CR, 29% | NR | NR |
| Pralatrexate (O'Connor et al.) [108] | 111 | ORR, 29%; CR, 11% | Median, 3.5 | Median, 14.5 months |
| Romidepsin (Coiffier et al.) [109] | 130 | ORR, 25%; CR, 15% | Median, 4 | |
| DHAP–alemtuzumab plus auto-SCT (Kim et al.) [110] | 24 | ORR, 50%; CR, 21% | NR | Median, 6 months |
| Gem–Cis–methylpred (Arkenau et al.) [111] | 16 | ORR, 69%; CR, 19% | NR | 69% at 1 year |
| PEGs (Mahadevan et al.) [112] | 33 ^a | ORR, 39% | 12% at 2 years | 30% at 2 years |
| Lenalidomide (Dueck et al.) [113] | 23 | ORR, 30% | Median, 3.2 | Median, 8 months |
| Zancolimumab (D'Amore et al.) [114] | 21 | ORR, 24% | NR | NR |

^aSeventy-nine percent were newly diagnosed.

Table 5. Recommendations published in the last 5 years for the management of NK/T-cell lymphomas

| | BJH, 2011 [117] | ESMO, 2013 [118] | SIE, SIES, GITMO, 2014 |
|---|--|---|--|
| Nodal T-cell lymphoma, intestinal and hepatosplenic T-cell lymphoma | <p>Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS): CHOP remains the standard therapy. Consideration should be given to consolidation with auto-haematopoietic stem cell transplantation (HSCT). Relapsed or refractory disease should be treated with relapse-schedule chemotherapy and considered for allo-HSCT.</p> <p>CNS prophylaxis should be considered</p> <p>Angioimmunoblastic T-cell lymphoma (AITL): Outside a clinical trial, CHOP or FC would be considered as standard therapy. Consolidation with auto-HSCT should be considered for chemosensitive diseases in first remission or after relapse. Routine CNS prophylaxis is not warranted.</p> <p>ALCL (anaplastic large-cell lymphoma): Patients with limited-stage ALCL and no adverse prognostic features by IPI should be treated with three to four cycles of CHOP chemotherapy and involved field radiotherapy. All other patients should receive six to eight cycles of CHOP chemotherapy. ALK-negative patients should be treated as for PTCL-NOS. Primary cutaneous ALCL (ALK negative) should be managed with local excision ± radiotherapy and chemotherapy reserved for those patients with systemic disease. At relapse, patients should receive platinum-based chemotherapy or an alternative salvage regimen and patients with chemosensitive disease should be considered for transplant.</p> <p>Enteropathy-associated T-cell lymphoma (EATL): CHOP like therapy, with or without an up-front autograft remains a common approach outside trial but evidence of efficacy is lacking and adoption of a more intensive approach, such as NCRI/SNLG protocol, is a reasonable option in fitter patients.</p> <p>Hepatosplenic T-cell lymphoma: allogeneic bone marrow transplantation could be considered but the evidence is purely anecdotal. Conventional chemotherapy approaches as for PTCL-NOS are the default, and there are some survivors reported in the literature.</p> | <p>First-line treatment of all TCL subtypes but NK/TCL, nasal type, should be based on anthracycline-containing regimens such as CHOP/CHOEP and CHOP-like regimens. An exception to this assumption could probably be made for EATL that has been treated with a specific regimen according to the Scottish Lymphoma Group. For patients with poor-risk TCL (IPI or PIT ≥ 2) with a chemosensitive disease (in CR or PR) after induction chemotherapy, autologous stem cell transplantation (ASCT) should be delivered.</p> <p>Second-line treatment of refractory/relapsed TCL should contain one or more than one among the following drugs: platinum, gemcitabine. Auto-SCT should be considered for relapsed/refractory TCL-NOS as well as ALK-negative ALCL and AITL.</p> <p>Allo-SCT in relapsed/refractory TCL (TCL-NOS, ALCL ALK- and AITL) proved to be the only curative treatment of this patient subset (provided by retrospective studies).</p> <p>Refractory relapsed TCL should be enrolled, whenever possible, in phase I or II prospective clinical trials aimed at exploring the efficacy of new drugs that have shown activity in preclinical studies.</p> | <p>In patients aged 65 years or younger, with nodal, intestinal or hepatosplenic T-cell lymphomas, except for ALK+ ALCL, six courses of CHOP or CHOEP (induction phase) followed by ASCT (consolidation phase) is the recommended therapy. For ALK+ ALCL patients with an IPI score lower than 3, the induction phase with CHOP or CHOEP × 6 courses without the consolidation phase is recommended.</p> <p>Patients older than 65 years, CHOP or CHOP-like regimens are the first therapeutic options. In patients fit to intensive chemotherapy, the approach used in younger patient can be considered.</p> <p>In patients with refractory or relapsed PTCL (excluding ALCL), platinum-based, ifosfamide-based, gemcitabine-containing chemotherapy, pralatrexate, romidepsin or bendamustine are the recommended therapies.</p> <p>The current evidence does not allow to make a choice among these agents.</p> <p>In refractory or relapsed ALCL, anti-CD30 (brentuximab-vedotin) monoclonal antibody should be preferred.</p> <p>Patients with chemosensitive disease should receive consolidation with allogeneic SCT. In the absence of a donor, autologous transplantation can be used.</p> <p>In non-transplant eligible patients, novel agents should be recommended, but these therapies should be considered as experimental and to be done within clinical trials.</p> |

Patients with localized disease should receive radiotherapy as early as possible at doses of at least 50 Gy to the tumour and adjacent structures. The evidence is not sufficient to routinely support CT concurrently or sequentially to RT. Patients with systemic disease should receive L-asparaginase-containing regimens. The SMILE protocol proved to produce the best results, although toxicity was not negligible. The use of ASCT should be considered during first complete remission. Radiotherapy should be added to areas of bulky or residual disease. Radiotherapy (20–30 Gy), possibly preceded by reductive surgery, should be recommended in patients with localized lesions. Pulse steroid therapy (0.6–0.7 mg/kg/die × 10 days every month prednisone or equivalent) should be recommended in patients with multiple non-contiguous lesions. Six courses of monochemotherapy with gemcitabine or peg-doxorubicin is an alternative option in patients with high tumour load.

For NK/T-cell nasal-type lymphoma, the treatment should include L-asparaginase and local (nasopharyngeal) radiotherapy.

In SPTCL without associated haemophagocytic syndrome (HPS), systemic steroids or other immunosuppressive agents should be considered first, whereas in cases of solitary or localized skin lesions, radiotherapy with electrons is advised. Little information on radiation dose is available, but a dose of 40 Gy has been used. Bexarotene may be also effective in SPTCL. Multi-agent chemotherapy is required only in cases with progressive disease not responding to immunosuppressive therapy or in cases with HPS.

Patients with localized disease should receive radiation with 50–55 Gy. The value of additional chemotherapy (CHOP, etoposide-based or asparaginase-based) remains unclear but is considered conventional pending more information. Asparaginase-containing regimens should be considered in relapsed or refractory disease. High-dose therapy is unproven, and there is no basis to recommend it outside trial.

CHOP-like chemotherapy appears to be effective and produces survivors. Relapse disease may respond to dose intensification in some patients. Local radiotherapy has a place for good prognosis localized symptomatic skin involvement which does not resolve with topical steroids.

Extranodal NK/T-cell lymphoma, nasal type

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) ($\alpha\beta$ only)

based on evidence from CTCL. The EP judged that the scant literature could not support evidence-based recommendations.

Recommendations
Radiotherapy (20–30 Gy), possibly preceded by reductive surgery, should be recommended in patients with localized lesions.
Pulse steroid therapy (0.6–0.7 mg/kg/die ×10 days every month prednisone or equivalent) is recommended in patients with multiple non-contiguous lesions.
Six courses of monochemotherapy with gemcitabine or peg-doxorubicin is an alternative option in patients with high tumour load.

issue 6: first-line therapy in advanced CTCL (consensus-based recommendations)

Several large retrospective studies consistently documented clinical RRs with total skin electron beam irradiation (TSEBI), i.e. ionizing radiation to the entire skin surface, as high as 100% in T2/T3 mycosis fungoides (MF) with relevant improvement of symptoms and quality of life [86–90], and short response duration in T3 MF with cosmetic adverse effects.

Cytotoxic regimens has been proven to prolong OS in advanced-stage CTCL; therefore, immunomodulatory therapies are preferred for first-line systemic treatment. Interferon alpha-2b achieves 60%–100% RR in stage IIB–IVA disease: higher rates are allowed by the association with psoralens plus ultraviolet A [91]. Bexarotene did not prove to achieve better RRs than CT [92]. Indeed, with gemcitabine monotherapy a 68% RR has been reported both in untreated and in refractory patients with advanced CTCL [93]. Similar or higher rates were obtained with pegylated liposomal doxorubicin [94, 95]. Polychemotherapy never produced higher RRs than the above monochemotherapy regimens [96].

Extracorporeal photophoresis (ECP) produced RRs of 30%–70% which were greatly increased with the association with interferon, bexarotene or granulocyte-macrophage-colony stimulating factor [97–99]. However, the evidence that ECP improves both RRs and OS in the setting of refractory erythrodermic CTCL was judged of low quality [100]; therefore, the EP did select ECP as a first-line treatment.

Three histone deacetylase (HDAC) inhibitors were tested: romidepsin, vorinostat and denileukindifitox. The former achieved RRs of 34% in two large phase II studies [101, 102]. Both vorinostat and denileukin difitox achieved 30%–44% responses in a phase III and some phase II trials [103–105].

A recent literature review retrieved scant retrospective data on allo-SCT in advanced CTCL [105] and no randomized study. However, retrospective data consistently showed [106] survival rates >50% at 3 years with non-myeloablative conditioning.

Recommendations
Total skin electron beam irradiation (TSEBI) ± boost is highly recommended first-line in skin-advanced cutaneous T-cell lymphoma.
Monochemotherapy is an alternative option in case TSEBI facilities are not readily available.
Different drugs have been proposed for this indication (gemcitabine, peg-doxorubicin, vorinostat, romidepsin, denileukindifitox, bexarotene), but there is no evidence of superiority for any of them.

Bexarotene should be recommended in patients refractory to or relapsing after first-line systemic treatment, and should also be used in patients obtaining at least stabilization after TSEBI or CT first line.
Enrolment in clinical trials should be recommended whenever possible.
Young patients responding to first-line treatment should be considered, at least in selected cases, for HSCT procedures.

issue 7: monitoring the response to first-line therapy (consensus-based recommendations)

Recommendations
In PTCL, re-evaluation should be carried out after three cycles of chemotherapy to define primary refractory disease.
In PTCL nasal type, the re-evaluation should be done after two cycles of the SMILE regimen. EBV-DNA quantitative assay could be used during treatment to predict therapy outcome.
In CTCL, re-evaluation should be done 6 weeks after the completion of TSEBI or after three cycles of monochemotherapy.
PET/CT scan has been proposed as useful tool for early response evaluation in PTCL, but it should be discouraged outside clinical trials since no validated reporting rules are available.

issue 8: therapy for non-responding or relapsed patients (consensus-based recommendations)

Relapsed/refractory disease is common for most patients with PTCL who receive current agents with inadequate salvage therapy. An array of new agents have been tested with early phase trials in non-responding or relapsed patients. A number has been proven to be effective (Table 4) [107–114].

The role of allo- and auto-transplantation in patients with advanced disease has been retrospectively studied in 77 and 241 patients with PTCL [115, 116]. Three-year PFS and OS of ASCT recipients beyond first complete remission were 42% and 53%, respectively. Among allo-SCT recipients who received transplantations beyond first complete remission, 31% remained progression-free at 3 years, despite being more heavily pre-treated and with more refractory disease. Non-relapse mortality was 3.5-fold higher for allo-SCT. In multivariate analysis, chemotherapy sensitivity and two or fewer lines of pre-transplantation therapy were prognostic of survival. These data suggest greater effectiveness of SCT earlier in the disease course and limited utility in mutiply relapsed disease.

Recommendations
In patients with refractory or relapsed PTCL (excluding ALC), platinum-based, ifosfamide-based, gemcitabine-containing chemotherapy, pralatrexate, romidepsin or bendamustine are the recommended therapies.
The current evidence does not allow to make a choice among these agents.
In refractory or relapsed ALCL, anti-CD30 (brentuximab-vedotin) monoclonal antibody should be preferred.
Patients with chemosensitive disease should receive consolidation with allo-SCT. In the absence of a donor, ASCT can be used.
In non-transplant eligible patients, novel agents should be recommended, but these therapies should be considered experimental and to be done within clinical trials.

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Table 6. Recommendations published in the last 5 years for the therapy of advanced primary cutaneous T-cell lymphomas

| ESMO, 2013 (119) | SIE SIES, GITMO, 2014 |
|--|---|
| In patients with advanced and refractory disease, gemcitabine or liposomal doxorubicin may be considered. Other agents like the fusion toxin denileukin diftitox and histone deacetylase inhibitors, such as vorinostat and romidepsin, have been approved in the United States, but have not yet been registered for cutaneous T-cell lymphoma in Europe. | Total skin electron beam irradiation (TSEBI) ± boost is highly recommended first-line in skin-advanced cutaneous T-cell lymphoma. |
| Multi-agent chemotherapy is only indicated in patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumour stage MF which cannot be controlled with skin-targeted and immunomodulating therapies. | Monochemotherapy is an alternative option in case TSEBI facilities are not readily available. |
| Local palliation of cutaneous as well as extracutaneous lesions may be achieved with local radiotherapy to doses ≥8 Gy. | Different drugs have been proposed for this indication (gemcitabine, peg-doxorubicin, vorinostat, romidepsin, denileukindifitox, bexarotene), but there is no evidence of superiority for any of them. |
| In relatively young patients with refractory, progressive mycosis fungoides or with Sezary syndrome allogeneic stem cell transplantation may be considered. Durable responses have been reported, but experience is still limited, and the optimal conditioning regimen and the optimal timing for an allogeneic transplant are currently unknown. | Bexarotene should be recommended in patients refractory to or relapsing after first-line systemic treatment, and should also be used in patients obtaining at least stabilization after TSEBI or chemotherapy first line. |
| | Enrolment in clinical trials should be recommended whenever possible. |
| | Young patients responding to first-line treatment should be considered, at least in selected cases, for HSCT procedures. |

discussion

In this project, we used a rigorous appraisal of evidence for providing specific evidence-based recommendations on management of PTCL according to GRADE methodology. This system was applicable to a limited number of issues in which a preliminary judgement of the quality of evidence and a subsequent assessment of the strength of the recommendation based on a qualitative risk-benefit analysis was provided [4]. For the remaining key issues, we adopted the group discussion methodology and we provided consensus-based recommendations.

Few other guidance, projects have been published for these rare lymphomas. The British Committee for Standards in Haematology has produced in 2011 guidelines for the management of mature T-cell and NK-cell neoplasms, excluding CTCLs [117]. In 2013, the European Society of Medical Oncology (ESMO) organized consensus conferences to focus on specific issues in different lymphomas, including PTCL [118, 119]. The recommendations on therapy are reported in Tables 5 and 6.

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