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POSITION PAPER

Diagnosis, management and follow up of peripheral T-cell lymphomas: a consensus practice statement from the Australasian Lymphoma Alliance

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Abstract

Peripheral T-cell lymphomas (PTCL) represent a heterogeneous disease group accounting for 10% of non-Hodgkin lymphomas. PTCL patients have typically poorer outcomes compared with aggressive B-cell lymphomas. However, such outcomes are heavily dependent on subtype. Although anthracycline-based regimens such as cyclophosphamide, doxorubicin, vincristine and prednisone remain the standard first-line treatment for most aggressive PTCL, there are important variations including incorporation of novel agents, use of radiotherapy and judicious consideration of stem cell transplantation. Relapsed or refractory disease represents a significant area of unmet need where chemotherapy intensification has limited efficacy and novel agents such as brentuximab vedotin and pralatrexate provide additional opportunities for attainment of remission and potential stem cell transplant. In the future, pre-therapy prognostic biomarkers including genomic characterisation, may aid in risk stratification and help guide initial patient management to improve survival. There is an urgent need to understand better the pathogenesis of PTCL to facilitate novel drug combinatorial approaches to improve survival. This position statement represents an evidence-based synthesis of the literature for application in Australian and New Zealand practice.

Introduction

Peripheral T-cell lymphomas (PTCL) are a heterogeneous category of mature, typically nodal lymphomas arising from post-thymic (i.e. 'peripheral') T-cells[1] with typically aggressive clinical courses. This position statement addresses the management of the major nodal and extranodal PTCL.

Methodology

This Consensus Practice Statement was undertaken by a panel of lymphoma experts with particular interest in PTCL under the auspices of the Australasian Lymphoma Alliance (ALA) in accordance with the ALA Consensus Practice Statement development policy. The relevant literature was reviewed by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Tables 1 and 2. Statements without

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Table 1 Levels of evidence

Level	Body of evidence
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A trial with an independent blinded comparison with a valid reference standard
III-2	A comparative study with concurrent controls, for example, nonrandomised trial, cohort or case control study
III-3	A comparative study without concurrent controls, for example, historical control study, or two or more single arm study
IV	Case series with post-test outcomes

Adapted from NHMRC Evidence Hierarchy Table 2009.

Table 2 Grades of recommendation

Grade of recommendation	Description
A	Body of evidence can be trusted to guide clinical practice
B	Body of evidence can be trusted to guide clinical practice in most situations
C	Body of evidence provides some support for recommendation(s), but care should be taken in its application
D	Body of evidence is weak, and recommendation must be applied with caution

grading were considered justified standard clinical practice by the experts and the ALA members. Feedback from key stakeholders was also sought.

Epidemiology/clinical presentation

PTCL represent 5–15% of non-Hodgkin lymphomas.[1] Nodal subtypes predominate and frequently present with B-symptoms, advanced stage and extranodal involvement. The most frequent subtype, PTCL not otherwise specified (PTCL NOS), is a heterogeneous category of nodal and extranodal mature T-cell lymphomas that do not correspond to any of the specifically defined entities of mature T cell lymphoma in the current classification.[1] It is a diagnosis of exclusion, represents 20–40% of all PTCL with a median age of 60 years.[2] Angioimmunoblastic T-cell lymphoma (AITL) represents approximately 20% of PTCL with a median age of 60–65 years[3] and is the most common subtype of PTCL of follicular T helper origin. It is often associated with a subacute systemic prodrome that may mimic infection or autoimmune disease and lead to a delay or misdiagnosis. Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) is more commonly seen in young adults (median age 30 years), whereas ALK-negative ALCL occurs in older adults (median age 55 years).[4,5] Extranodal subtypes include enteropathy-associated T-cell lymphoma (EATL) and extranodal NK/T-cell lymphoma (NKTCL). EATL is usually associated with coeliac disease. Patients are frequently aged in their 60s and present with pain, perforation or obstruction from bowel involvement. NKTCL is strongly associated with Epstein–Barr virus (EBV) infection and most commonly seen in Asia with a predilection for the nasal/sinus region.

Diagnosis

Diagnosis of PTCL requires correlation of clinical, histological, immunophenotypic, cytogenetic and molecular information. Correct subclassification is important to rationalise access to novel agents and clinical trial enrolment. Classification is challenging with consensus ranging from 67% to 95% among expert haematopathologists.[2,6] Surgical biopsy is recommended for adequate tissue for assessment. Immunohistochemistry is usually more extensive than for other lymphomas. Typical work up includes pan T-cell antigens (CD2, CD3, CD5, CD7), T-cell subsets (CD4, CD8), T follicular helper cell antigens (CD10, PD1), follicular dendritic antigens (CD21, CD23, CD35), B-cell antigens (CD20), EBV, CD30 and ALK-1. Molecular testing using polymerase chain reaction assessment of clonal T-cell receptor (TCR) rearrangements has traditionally been used, but such assays lack both sensitivity and specificity. Demonstration of TCR clonality is not synonymous with malignancy as this may be observed in reactive conditions.

A variety of fluorescence *in situ* hybridisation probes are used for PTCL, most commonly to provide prognostic information in ALK-negative ALCL. Two mutually exclusive and clinically significant rearrangements have been described in this tumour involving the *DUSP22-IRF4* locus and the *TP53* homologue *TP63*, identifying favourable and adverse prognostic groups respectively.[7] The so-called triple negative group (negative for *ALK*, *DUSP22* and *TP63* rearrangements) may also prove to be biologically mixed.[8]

Next-generation sequencing holds promise to improve the diagnosis, subclassification and prognostication of PTCL. The detection of mutations for sequence variants such as *TET2/DNMT3A/IDH2* is becoming more readily available in the routine work up of suspected PTCL.[9–12]

Recommendation

Surgical biopsy and multidisciplinary review including an expert lymphoma pathologist are recommended to

ensure the correct PTCL subclassification for treatment planning, rationalising access to novel agents and clinical trial enrolment.

Staging

Identification of B symptoms, physical examination and laboratory tests including full blood examination, hepatic and renal testing, lactate dehydrogenase (LDH) and screening for human immunodeficiency virus, Hepatitis B and C are required. Almost all PTCL are avid with ^{18}F-fluorodeoxyglucose positron emission tomography (PET).[13,14] All patients should be preferably staged with PET/computed tomography (CT), if available, at diagnosis.[15] Bone marrow biopsy is required for staging purposes, to assess haemopoiesis and the presence of haemophagocytic syndrome. Lumbar puncture and magnetic resonance imaging (MRI) are required if central nervous system involvement is suspected. Staging is performed according to the Ann Arbor classification.[15] MRI and endoscopic evaluation are important in NKTCL for staging and radiotherapy (RT) planning.

Recommendation

All patients should be preferably staged with PET/CT, if available, and bone marrow biopsy.

Prognostic factors

The prognosis of PTCL is determined by the specific histological subtype. The International Prognostic Index (IPI) has been validated in PTCL[16] and is the most widely used tool. Several alternative PTCL-specific tools have been developed, including the prognostic index for T-cell lymphoma (PIT),[17] the modified PIT,[18] a PTCL-NOS specific score,[19] age-adjusted IPI[20] and the Glasgow prognostic score.[21] Few of these prognostic scores have been adopted in routine practice. For practical purposes, the IPI remains a recommended tool.

Recommendation

The IPI remains useful across PTCL subtypes.

Management

First-line treatment: PTCL NOS, AITL, ALCL

First-line treatment should be tailored to a patient's age, fitness and co-morbidities. Given the rarity of PTCL and poorer outcomes, clinical trial participation should be considered the standard of care where available. Our recommended treatment algorithm is shown in Figure 1. The initial goal is to achieve long-term remission or cure. Historically, first-line therapy for nodal PTCL has been identical across histological subtypes. Most evidence comes from retrospective PTCL studies or subgroup analyses[22] of prospective trials of aggressive B- and T-cell lymphomas with inadequate statistical power to determine T-cell specific outcomes.[23]

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-based chemotherapy evolved as standard of care for PTCL based on extrapolation of treatment paradigms for aggressive B-cell lymphomas.[23] The International PTCL project reported 5-year OS rates of 32% for PTCL NOS, 33% for AITL, 70% for ALK+ ALCL and 49% for ALK− ALCL in patients treated primarily with CHOP-based regimens.[2] While outcomes were comparable with non-anthracycline-based regimens, this was a retrospective analysis and treatment decisions are likely to have been influenced by patient factors. Reducing the time interval from 3 to 2 weeks (CHOP-21 vs CHOP-14) or administering eight instead of six cycles of chemotherapy did not improve event-free survival (EFS) or overall survival (OS) in elderly patients.[22]

The main regimen purported to offer benefit over CHOP is CHOP plus etoposide (CHOEP) but is yet to be tested in a prospective trial. In an initial retrospective analysis of CHOEP in selected PTCL patients (age <60 years, normal LDH), the addition of etoposide improved EFS but not OS.[22] Similarly, the Swedish registry demonstrated improved progression-free survival (PFS) but not OS for patients aged <60 years.[24] Conversely, outcomes were not improved in a meta-analysis[25] or a national registry analysis.[26] The use of dose-escalated CHOEP (high-CHOEP) or a mega-dose (MegaCHOEP) variant, which incorporated stem cell rescue[22] or hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine),[27,28] also demonstrated no improved OS over CHOP.

Other chemotherapy regimens have not proven superior to CHOP. Randomised controlled trials (RCT) comparing GEM-P (gemcitabine, cisplatin, methylprednisolone) or VIP (etoposide, ifosfamide, cisplatin)/ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) with CHOP did not demonstrate improved complete remission (CR) rates (CHOP 62% vs GEM-P 46%; $P = 0.16$) or 2-year EFS (CHOP 45% vs VIP/ABVD 41%; $P = 0.7$).[29,30]

Brentuximab vedotin (BV) is an antibody drug conjugate consisting of an anti-CD30 monoclonal antibody conjugated to a microtubule inhibitor, monomethyl auristatin E. BV-CHP (cyclophosphamide, doxorubicin, prednisone) demonstrated superior PFS compared with CHOP in CD30+ (defined as ≥10% of cells) PTCL.[31,32] Approximately 70% of patients had ALCL (ALK+ IPI 2–

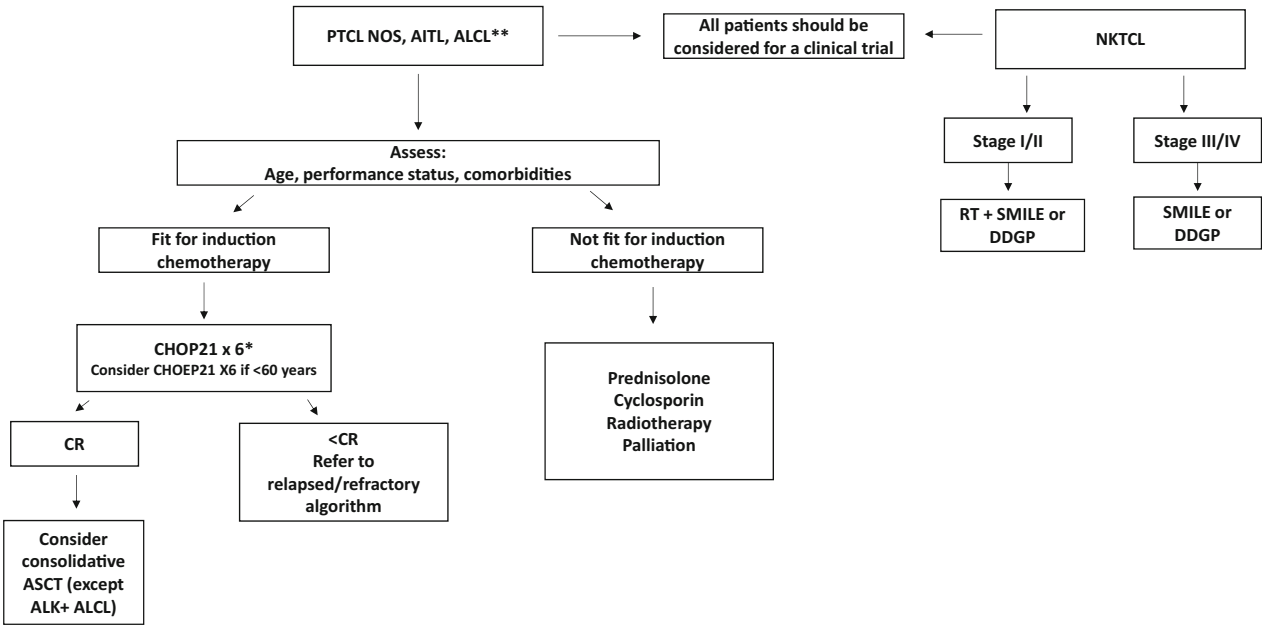

Figure 1 Algorithm for first-line treatment of PTCL by subtype. *Consolidative radiotherapy can be considered for patients presenting with stage I/II disease. **Brentuximab-vedotin (BV) + CHP is recommended for ALCL. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK+ ALCL, anaplastic lymphoma kinase-positive anaplastic large cell lymphoma; ASCT, autologous stem cell transplantation; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CR, complete remission; DGP, dexamethasone, asparaginase, gemcitabine, cisplatin; NKTCL, natural killer T-cell lymphoma; PTCL NOS, peripheral T-cell lymphoma not otherwise specified; RT, radiotherapy; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide.

5, ALK− ALCL) and an improved PFS was reported for this secondary end-point for receiving BV-CHP. Importantly, the study was not powered to assess PTCL subgroups such as PTCL-NOS or AITL. This is the first RCT to demonstrate improved PFS compared with CHOP in PTCL.

Recent studies investigating the addition of novel agents (alemtuzumab, bevacizumab, romidepsin) to CHOP have not demonstrated superiority over CHOP alone and were associated with increased toxicity.[33–38]

Recommendation

- CHOP every 21 days for six cycles is the recommended first-line treatment (II, A).
- Consideration may be given for CHOEP for patients aged <60 years with a normal LDH (III-2, C).
- Dose intensification beyond CHO(E)P is not recommended outside investigational studies (III-2, C).
- For all patients with ALCL, BV-CHP for six cycles is recommended, if funded and available (II, B).
- The benefit of the addition BV to chemotherapy in other CD30+ (defined as ≥10% of cells) PTCL subtypes is less clear due to small patient numbers. There is no evidence to support a role of BV in AITL. There is no recognised relationship between CD30 expression (≥10% of cells) and response to BV-CHP. Based on current evidence, outside the setting of a clinical trial, BV is not routinely recommended for non-ALCL subtypes but can be considered on a case-by-case basis (II, C). Access to government-funded novel agents can vary within Australia (PBS) and New Zealand (Pharmac).

Role of radiotherapy in limited-stage PTCL

Following systemic therapy, consolidation RT is recommended for limited-stage (stage I/II) PTCL treated with curative intent. Although randomised evidence is lacking, retrospective series report clinically significant improvements in disease-specific survival, PFS and OS with consolidative RT in limited stage PTCL-NOS.[39–43] A recently published analysis using the National Cancer Database of 3670 patients with early stage PTCL-NOS and ALK negative ALCL reported an OS benefit favouring the addition of consolidation RT (HR 0.69 (95% confidence interval (CI): 0.58–0.84; $P < 0.01$) on multivariate analysis.[41] Furthermore, data analysed from the Surveillance, Epidemiology, and End Results (SEER) database revealed an improvement in 5-year OS from 35% to 59% with the addition of RT in patients with

limited-stage PTCL-NOS (HR 0.527; 95% CI: 0.427–0.651; $P < 0.001$).[43] There is no evidence for an adapted PET-guided approach for the omission of RT in limited stage PTCL.

In RT planning, expert opinion favours the use of involved node radiotherapy (INRT)/involved site radiotherapy (ISRT) for limited stage PTCL, to reduce the risk of RT-induced toxicities.[44–46] Principles of INRT/ISRT are described by the International Lymphoma Radiation Oncology Group.[45,47,48] Pre-chemotherapy PET/CT imaging is strongly recommended for accurate target delineation and optimally performed in the RT treatment position.[47] Limited data exist for the dose responsiveness of PTCL. Based on expert opinion, recommended doses for consolidation RT are 30–40 Gy, delivered in conventional fraction sizes of 1.8–2 Gy.[19,45,49] Higher doses of 40–50 Gy may be considered for sites achieving partial response to frontline chemotherapy.[19,45]

Recommendation

- Consolidative RT is recommended for limited-stage PTCL (III-2, C).
- There is no evidence that chemotherapy can be safely abbreviated in limited stage PTCL if RT is used (III-2, C).

Role of autologous transplantation in first remission

Consolidation with high-dose chemotherapy (HDT)/autologous stem cell transplantation (ASCT) aims to reduce the high relapse rate following first complete remission (CR1) with CHOP-based chemotherapy. Prospective data reporting outcomes with CHOP represent the most appropriate 'benchmark' to compare HDT/ASCT studies. Recent prospective studies have demonstrated 3-year PFS on 28–44% for patients receiving CHOP chemotherapy.[31,50]

Two phase II studies examined the role of consolidative HDT/ASCT. The Nordic Lymphoma Group (NLG-T-01) reported 5-year PFS of 44% and OS of 55% with CHOEP + BEAM or BEAC HDT/ASCT.[51] A German study used CHOP21 + dexaBEAM then total body irradiation/cyclophosphamide or BEAM HDT/ASCT and reported a 5-year PFS of 36% and OS of 48%.[52] Importantly, 25–30% of patients failed to proceed to ASCT in these studies, mostly due to refractory or progressive disease. Patients with ALK+ ALCL were excluded from both studies on the basis of favourable outcomes with chemotherapy alone.[2,22] Other studies have not clearly demonstrated a survival benefit, with physician bias limiting the interpretation of results.[53,54]

Outcomes following consolidative HDT/ASCT purport to be superior to chemotherapy alone.[2,3,39,55] Despite the lack of a RCT, guidelines recommend considering HDT/ASCT in CR1 for PTCL other than standard-risk ALK-positive ALCL.[44,56,57] The major arguments against consolidative HDT/ASCT are the absence of RCT data and possible selection biases limiting non-randomised studies. A RCT compared consolidative ASCT with allogeneic SCT (AlloSCT) and demonstrated similar EFS with more deaths from relapse in the ASCT group and more deaths from toxicity in the AlloSCT group.[58] These data confirm a graft-versus-lymphoma effect in PTCL.

Recommendation

- Consolidative ASCT could be considered for AITL, PTCL NOS and ALK-negative ALCL (III-3, C).
- Consolidative ASCT is not recommended for standard-risk ALK+ ALCL (III-3, C).
- If considering consolidative transplantation, ASCT is recommended over AlloSCT due to the high treatment-related mortality and similar outcomes (II, C).

Relapsed/refractory PTCL treatment

Patients with relapsed/refractory (RR) PTCL have a poor prognosis with a median OS of approximately 6 months and 3-year overall survival of approximately 20%.[59] Moreover, the pathology and biology of PTCL is complex and may evolve over time. Our recommended treatment algorithm is shown in Figure 2.

Recommendation

- Repeat biopsy of RR disease is highly recommended prior to initiation of salvage therapy (IV, A).
- We encourage presentation of all cases to local and national multidisciplinary team meetings and participation in clinical trials (IV, A).

Anaplastic large cell lymphoma

The use of BV in RR ALCL is supported by a phase II trial where the 5-year OS was 60%.[60] No survival differences were detected between patients with ALK-positive and ALK-negative status. Patients in CR who received ASCT experienced improved 5-year PFS but no difference in OS compared with eligible patients who were not transplanted. The benefit of consolidative ASCT for such patients is unclear and should be performed at the clinician's discretion. Retreatment with BV can be effective in patients who have previously obtained a CR or partial remission to BV.[61] The $t(2;5)$ translocation leads to the

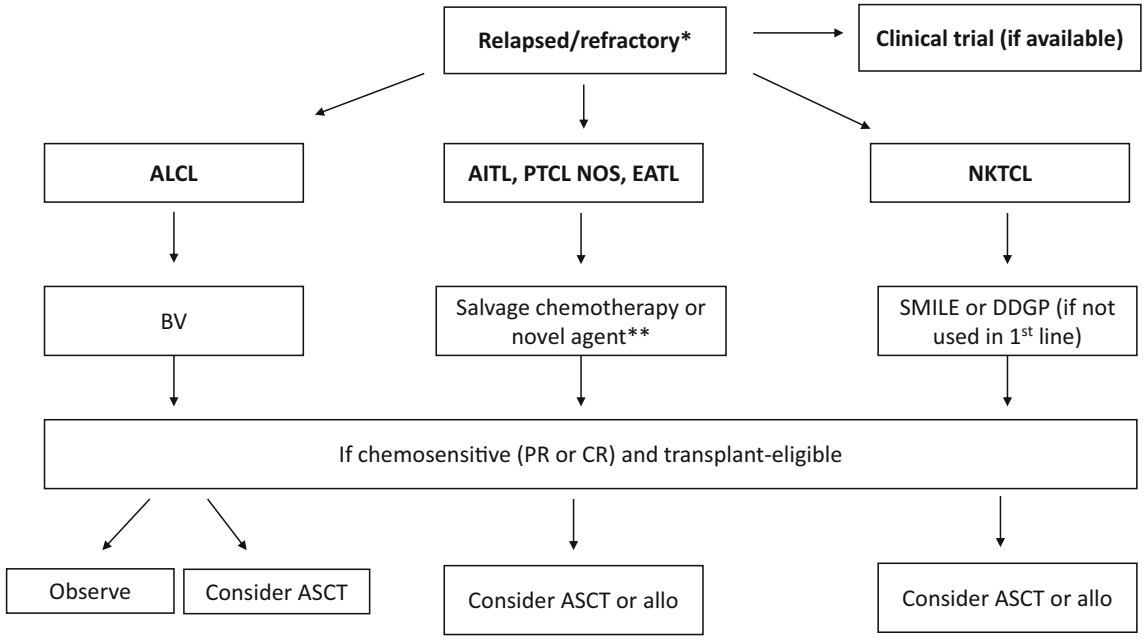

Figure 2 Algorithm for treatment of PTCL by subtype in the relapsed/refractory setting. *Patients not deemed eligible for these treatments can be considered for palliative options including radiotherapy, cyclosporin, prednisolone or best supportive care. **If available, options include pralatrexate, romidepsin or BV. AITL, angioimmunoblastic T- cell lymphoma; ALCL, anaplastic large cell lymphoma; allo, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; CR, complete remission; DGP, dexamethasone, asparaginase, gemcitabine, cisplatin; EATL, enteropathy-associated T-cell lymphoma; NKTCL, natural killer T-cell lymphoma; PR, partial remission; PTCL NOS, peripheral T-cell lymphoma not otherwise specified; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide.

formation of a novel *NPM-ALK* chimeric protein, which has constitutive tyrosine kinase activity.[62] Crizotinib is an oral ALK inhibitor that demonstrated activity in heavily pre-treated ALK-positive ALCL patients with an ORR was 90% (10/11) and 2-year OS of 72% and PFS of 63%.[63]

Recommendation

- BV is recommended as second line therapy in ALCL irrespective of ALK status (III-3, A).
- ALK inhibitors may be used in the RR setting in ALK-positive ALCL after BV (III-3, C).

PTCL-NOS and AITL

Optimal therapy for RR PTCL/AITL remains to be defined and is presently based on the goal of care, expected toxicities and patient comorbidities. There is consensus that ASCT should be attempted in eligible patients. The International PTCL Project identified that transplant-eligible patients who proceeded to ASCT had improved 3-year survival after relapse compared with those who did not (48% vs 27%).[59] In this analysis, those ineligible for ASCT had a 3-year survival of 7%.

Transplant-eligible patients

In patients proceeding to ASCT, salvage chemotherapy regimens have been investigated with no clear superiority of any regimen. The only RCT in this setting was a subgroup analysis of the LY.12 trial comparing GDP (gemcitabine, dexamethasone, cisplatin) with DHAP (dexamethasone, cytarabine, cisplatin), which did not identify significant differences in response rate, ASCT realisation rate, EFS or OS.[64]

Transplantation: autologous versus allogeneic

The CIBMTR reported outcomes of patients who underwent ASCT or AlloSCT for PTCL beyond CR1.[65] Three-year OS was 53% for ASCT and 46% for AlloSCT. Although AlloSCT recipients had more poor prognostic features, on multivariate analysis, AlloSCT was associated with higher non-relapse and overall mortality, without an associated reduction in relapse risk.

Transplant-ineligible patients

There is increasing evidence that outcomes may be improved by the earlier use of novel agents. When used

in first retreatment, analysis of the COMPLETE data identified a PFS benefit and the Columbia data demonstrated an OS benefit for patients receiving a novel agent over chemotherapy.[66,67] In transplant-ineligible patients or patients who have failed one line of salvage chemotherapy, we suggest a novel agent.

Novel agents

Pralatrexate

In the PROPEL phase II trial, pralatrexate (dihydrofolate reductase inhibitor) showed an overall response rate (ORR) of 29%, with a subset analysis suggesting improved ORR of 47% when used as second-line treatment post CHOP.[68,69] Concern has been raised about its efficacy in AITL but a phase I/II trial demonstrated an ORR 45%.[70] The Columbia regimen uses pralatrexate weekly for 3 weeks in a 4-week cycle with leucovorin for mucositis prophylaxis.[71] Leucovorin prophylaxis is associated with reduced rates of mucositis with no apparent impact on efficacy.[72] Stem cell collection and transplantation remains feasible.[69]

Brentuximab vedotin

BV possess modest activity in non-ALCL CD30+ nodal PTCL with an ORR of 41% in a phase II trial.[73]

Histone deacetylase inhibitors

In a phase II study, romidepsin demonstrated an ORR of 25% including 15% CR/CR unconfirmed. There was no difference in response rate based on the number of prior lines of therapy.[74]

Hypomethylating agents and 'epigenetic combinations'

AITL has a high frequency of mutations in genes regulating DNA methylation (*TET2*, *DNMT3A* and *IDH2*) that may correlate with responses to epigenetically targeted drugs such as hypomethylating agents and histone deacetylase inhibitors. However, patients without such mutations may also respond to epigenetic therapy and so the utility of mutation detection in therapeutic decisions is guarded.[75] A subset of PTCL patients may have concurrent manifestations of clonal haemopoiesis such as myelodysplastic syndromes.[76] Combination 'novel-novel' strategies are now being evaluated and hold promise including pralatrexate/romidepsin and romidepsin/azacitidine.[77,78]

Cyclosporin

In a subset of patients, PTCL behaves in an indolent fashion with slow disease kinetics and a relapsing/remitting course. This is more commonly seen with AITL where modulating T-cell activation with cyclosporin has been hypothesised to be able to control disease. A retrospective study in AITL patients identified an ORR of 67%.[79]

Role of radiotherapy in relapsed/refractorydisease

RT may be considered for local disease control. Expert opinion recommends RT doses of 30–36 Gy for sites of complete response following salvage therapy, 40–45 Gy to sites of incompletely responding residual disease and 45–55 Gy to sites of chemo-refractory progressing disease.[45] For patients with localised disease who relapse and are unfit for chemotherapy, definitive RT doses of 45–55 Gy may be considered for local control.[45] For patients requiring palliative-intent symptom control only, lower doses of RT are recommended: a standard hypofractionated course of 30 Gy in 10 fractions is acceptable.

Recommendation

- There is no standard of care for second line regimens and acceptable choices include combination chemotherapy or novel agents. Selection of second line therapy is dependent on intent of therapy, comorbidities and transplant eligibility (III-2, C).
- Novel agents should be considered in patients who are transplant eligible and have received ≥2 lines of chemotherapy or who are transplant ineligible and have received ≥1 of chemotherapy (III-2, C).
- Access to government-funded novel agents can vary within Australia (PBS) and New Zealand (Pharmac).
- In eligible chemotherapy-sensitive patients who have not previously had a stem cell transplant, we recommend ASCT over AlloSCT (III-2, B).
- Eligible patients who have relapsed following ASCT should be considered for AlloSCT (III-2, C).

Extranodal NK/T cell lymphoma (NKTCL)

Newly diagnosed limited stage (stage I/II) disease

Outcomes with CHOP chemotherapy are poor.[80] Non-anthracycline protocols have been shown in a retrospective study to improve PFS and OS but there have been no RCT examining individual chemotherapy and RT protocols.[81] There are multiple non-anthracycline regimens available (SMILE, DDGP, DeVIC, VIPD, GELOX) with no RCT to guide treatment.[82–84] Combined modality therapy (CMT, chemo-radiotherapy) can be performed either with

a concurrent or sequential approach, with no OS difference between the two strategies with non-anthracycline containing regimens.[85] Pre-chemotherapy PET/CT, MRI and endoscopic evaluation are strongly recommended for target volume delineation pre-RT. In those unfit for CMT, RT alone (50–60 Gy) is recommended.

Recommendation

- CMT is recommended for limited stage disease. CMT with non-anthracycline containing chemotherapy can be delivered in either a sequential or concurrent approach; choice of protocol has to factor in patient fitness and treatment unit familiarity (III-2, B).
- For patients unfit for CMT, RT alone is acceptable (III-2, B).

Newly diagnosed advanced stage (stage III/IV) disease

The optimal treatment strategy for advanced stage NKTCL has not been defined; however, CHOP-based therapy is not recommended due to lack of efficacy. A RCT comparing six cycles of DDGP (dexamethasone, gemcitabine, cisplatin, pegasparaginase) versus SMILE (dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide) demonstrated a 5-year OS benefit in favour of DDGP.[86] Caveats to interpretation of this study are that the optimal number of cycles of SMILE has not been established and asparaginase dosing differed between this RCT and early SMILE trials. A modified SMILE protocol has been developed utilising pegasparaginase.[87]

The role of consolidative ASCT in first-line therapy is uncertain given the absence of high-quality evidence in patients receiving asparaginase-based protocols. The CIBMTR identified patients having an AlloSCT in first-line therapy did not have superior survival to those receiving AlloSCT in later lines of therapy.[88]

Recommendation

- Asparaginase-based therapy is considered standard of care with DDGP preferred over SMILE (II, B).
- Consolidative stem cell transplantation is not recommended (III-2, B).

Relapsed/refractory disease

Examples of therapies used include DDGP, SMILE and AspaMetDex (L-asparaginase, methotrexate, dexamethasone).[84,89,90] For those refractory to asparaginase-based therapy, immune checkpoint inhibitors have shown encouraging activity in case series.[91,92]

Recommendation

- Patients who relapse following non-asparaginase-based therapies should have treatment with asparaginase-based protocols and be considered for transplantation (III-2, B).
- For patients refractory to asparaginase-based therapies, no standard of care is established. Immune checkpoint inhibitors display promise but require further study (IV, C).

Enteropathy-associated T-cell lymphoma (EATL)

EATL (previously type I) is a recognised complication of coeliac disease and should be considered in refractory coeliac disease/gluten enteropathy. Monomorphic epitheliotropic intestinal T-cell lymphoma, previously known as type II EATL, occurs in patients with no clear association with coeliac disease. Surgical resection may be required if extensive disease is present or there is risk of obstruction, haemorrhage or perforation. Surgical resection may also be considered for unifocal disease. Nutritional supplementation with total parenteral nutrition is an important part of care as malnourishment contributes to treatment failure. Outcomes with CHOP are poor (median OS <1 year).[93–97] Limited data suggest the CHOP/IVE/MTX (ifosfamide, vincristine, etoposide, methotrextate)-ASCT protocol has been associated with superior outcomes where deliverable.[93]

Recommendation

- A multidisciplinary approach with surgery, nutritional support and systemic therapy is required.
- CHOP, CHOEP or IVE/MTX-ASCT could be considered for front-line treatment based on age, comorbidities and performance status (III-2, C).

PTCL response assessment and follow up

As almost all PTCL are FDG-avid,[13,14,98,99] all patients should undergo end-of-treatment assessment with PET/CT, where feasible. There is insufficient evidence for interim PET/CT and response adapted therapy; however, where available, interim PET/CT is preferred to CT to improve the detection of disease in certain sites (e.g. gastrointestinal sites, skin). Results of PET/CT imaging should be reported using the five-point Deauville score in accordance with current Lugano international lymphoma guidelines.[15] Sites of residual metabolic activity on end-of-treatment PET/CT should be investigated further with biopsy (preferred) or serial follow-up

imaging prior to further treatment decisions. Bone marrow biopsy should be repeated for patients with initial involvement. In accordance with international guidelines for other aggressive lymphomas, follow up should be performed every 3 months for the first 2 years from diagnosis, 6 monthly for the next 3 years, then annually to detect relapse and assess for treatment-related adverse events.[15] Routine surveillance imaging is not recommended.

Recommendation

- End-of-treatment PET imaging should be performed, where feasible (III-2, C).
- Patients with positive bone marrow biopsy at diagnosis should have an end-of-treatment bone marrow biopsy (III-2, C).
- For patients achieving complete remission, surveillance imaging is not recommended (III-3, C).

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