CURRENT TREND

Enteropathy-associated T-cell lymphoma: A review on clinical presentation, diagnosis, therapeutic strategies and perspectives☆

Lymphomes \( T \) intestinaux associés à une entéropathie (maladie cœliaque et sprue réfractaire): présentation, diagnostic, prise en charge thérapeutique, pronostic et perspectives


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Available online 2 November 2010

DOI of original article:10.1016/j.gcb.2010.01.021.

Abbreviations: AB, antibodies; AIILD, angioimmunoblastic lymphadenopathy; ASH, American Society of Hematology; auto-PBSCT, autologous peripheral blood stem cell transplantation; CD, celiac disease; CD (preceding a number), cluster of differentiation; CE, capsule endoscopy; CR, complete remission; CT, chemotherapy; CTS, computed tomography scan; DHFR, dihydrofolate reductase inhibitors; EATL, enteropathy-associated T-cell lymphoma; EBM, evidence-based medicine; ENT, ear, nose and throat; FACS, flow cytometry; FISH, fluorescence in situ hybridization; G-CSF, granulocyte colony-stimulating factor; GFD, gluten-free diet; GI, gastrointestinal; HDAC, histone deacetylase; HLA, human leukocyte antigen; iCD3, intracytoplasmic CD3; IECs, intestinal epithelial cells; IELs, intraepithelial lymphocytes; IFN-\( \gamma \), interferon gamma; IL-15, interleukin 15; IMiDs, immunomodulatory family of drugs; JNK, c-jun N-terminal kinase; NHL, non-Hodgkin’s lymphoma; mTor, mammalian target of rapamycin; PBSC, peripheral blood stem cells; PET-CT, positron emission tomography with CT scan; PFS/RFS, progression-free/relapse-free survival; PR, partial response; PS, performance status; PTCL, peripheral T-cell lymphoma; RCD, refractory celiac disease; RR, relative risk; SUV, standard uptake value; TCR, T-cell receptor; TGF-\( \beta \), transforming growth factor beta-1; TNF-\( \alpha \), tumour necrosis factor alpha; TTG, tissue transglutaminase; VA, villous atrophy; vs., versus.

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doi:10.1016/j.gcb.2010.09.008
Summary

Introduction. — Enteropathy-associated T-cell lymphoma (EATL) is a rare complication of celiac disease (<1% of lymphomas) and has a poor prognosis.

Methods. — International literature review with PubMed search (up to January 2009) of pathophysiological, clinical and therapeutic data.

Results. — EATL is found in patients with a mean age of 59 years, often with a complication that signals its diagnosis. Refractory celiac disease (RCD), equivalent to low-grade intraepithelial T-cell lymphoma, could be an intermediary between celiac disease and high-grade invasive T-cell lymphoma. The median survival is 7 months, with no significant difference between stages; the cumulative 5-year survival is less than 20%. The poor prognosis is determined by disease that has often spread before it is diagnosed (50%), multifocal involvement of the small bowel (50%), poor general health status and undernutrition, and recurrence of complications (infections, perforations, gastrointestinal haemorrhages, occlusions), thus delaying the chemotherapy and contributing to frequent chemotherapy resistance. There is currently no effective and consensual treatment: preventive surgery for complications is controversial, and the results of chemotherapy are disappointing. The classic CHOP protocol (combination of doxorubicin—cyclophosphamide—vincristine—prednisone) does not have satisfactory results and survival remains poor, especially in patients with underlying RCD. High-dose chemotherapy with autotransplantation seems to only improve the prognosis in localised forms. Allogeneic bone marrow transplantation was not evaluated. In all, 1/3 of patients, being unfit for treatment, die before 3 months and half of treated patients stop chemotherapy prematurely due to inefficacy, intolerance and/or complications.

Conclusion. — Improvement of the prognosis requires collaboration in order to compose a national cohort, to evaluate new diagnostic and therapeutic strategies and to define prognostic factors.

Introduction

Enteropathy-associated T-cell lymphoma (EATL) has been recognised since 2001 in the World Health Organisation’s (WHO) international classification of tumours of haematopoietic and lymphoid tissues as a separate entity from T-cell lymphomas [1,2]. The main characteristic of EATL besides its extreme rarity (less than 1% of all non-Hodgkin’s lymphomas [NHL]) [3] and its location in the intestine is that it is associated with an enteropathy and develops from the intraepithelial T-lymphocytes of the intestine. This NHL can occur as a complication of a previously recognised enteropathy or may signal its presence, and its diagnosis is thus based mainly on intestinal mucosa lesions seen at some distance from the lymphoma. The most classic form of EATL is type I (80%), which is a serious complication of celiac disease (CD). CD is the only enteropathy that is associated with this particular NHL and the molecular bonds have now been better described [4—6]. The other enteropathies in which EATL may be a complication have not been well characterised. EATL is not the only neoplasm to be associated with CD, e.g. other lymphomas, especially of B phenotype; gastric, colon and small bowel adenocarcinomas; oesophageal and ENT carcinomas [7—9], but their pathophysiological relationship has not been established. The therapeutic management of EATL remains particularly difficult and its prognosis is very poor.

Since 2008, the WHO classification [2] has individualised a minority (<20%) type II EATL that meets particular criteria, including the expression of CD56. Although they have been classified as EATL of the intestine, these type II EATL are less often associated with an enteropathy and do not have a proven genetic link with CD in half of the cases. A recent genetic study demonstrated that they occur via a distinct lymphomagenesis pathway [10]. They will be briefly described in the histology chapter, with the main part of the review and publications focusing on the classic form of type I EATL, which is associated with CD.

The main characteristics of EATL that contribute not only to its severity, but also to the difficulties related to therapeutic management of the disease include [11—14]:

- very frequent multifocal involvement of the small intestine;
- a diagnosis usually made in an advanced stage of the disease (stage III/IV in 40—60% of cases) and as a surgical emergency (>40%), thus delaying initiation of the chemotherapy (CT), along with malnutrition related to the underlying enteropathy;
- the seemingly constant occurrence of one or several complications, often hastened by treatments-related cachexia;
- infections, particularly in the post-CT aplastic phase;
- gastrointestinal (GI) perforations and haemorrhages [15,16].

Finally the main therapeutic problem remains CT resistance, which is very common in this type of NHL. The prognosis remains extremely bleak at this time, with 1- and 5-year survivals between 31—39% and 11—20%, respectively [11—14].

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The aim of this review, which is documented exclusively from a PubMed search, is to report on the published knowledge to date in the international literature with regard to pathophysiology, presentation, progression and especially therapeutic management by displaying the current results of CT and high-dose CT. EATL seems to distinctly distinguish itself from other peripheral non-Hodgkin’s T-cell lymphomas by its extreme severity, the frequency of surgical complications, the major prognostic impact on undernourishment and the absence of scientifically validated treatment. This situation requires multidisciplinary involvement in order to improve the diagnosis, treatment and prognosis.

Background

In 1855, Sir W. Gull made the first observation of a syndrome-like association between malabsorption and lymphoma [17]. Sometime later, in 1962, CD was found to be the cause of this malabsorption, carrying the risk of malignant transformation [18]. In 1978, the disease was defined as a “malignant histiocytosis of the intestine”, with a histological description already very close to that currently used of infiltrating more or less stenosing and perforating involvement of the intestine by a polymorphic large cell NHL, sometimes occurring with eosinophil infiltrates and frequently with mesenteric lymph nodes involvement [19–21]. In 1985, Isaacsen et al. [22] showed the T phenotype of this lymphomatous proliferation, long overshadowed by the intestinal NHL group, designated “intestinal T-cell lymphoma” (with or without enteropathy) in the Revised European-American Lymphoma classification (REAL classification) [23–25]. Its origin in intraepithelial T-lymphocytes (IELs) of the intestinal mucosa was then recognised due to the HML1 immunostaining, currently named CD103, specifically distinguishing it from the other peripheral T-cell NHL [26]. EATL was only finally clearly identified later as part of the WHO classification of lymphomas in 2001. It was designated “enteropathy-type T-cell lymphoma” (ETCL), and then changed to the current designation of EATL in the more recent 2008 version [1,2,9,23,27]. It is in fact a separate T-cell NHL, as much in terms of its pathophysiology as in its progression and its prognosis.

More recently, refractory celiac disease (RCD) 2 was described as being a low-grade lymphoma restricted to the intraepithelial compartment that could be complicated by a more aggressive, more invasive and classic form of EATL [4,16,28]. Although the links of continuity between these transitional forms have now been well documented, it does not appear that RCD2 is an obligatory step.

Pathophysiology [29]

CD is a chronic inflammation of the small intestine secondary to gluten ingestion (wheat, rye, barley). The presence of repeated motifs rich in glutamine and proline make gluten proteins a privileged substrate for tissue transglutaminase (tTG). Due to its deamidation properties, tTG introduces negative charges into the gluten peptides, thus increasing their affinity for the peptide pocket of HLA-DQ2/DQ8 molecules and promoting the formation of stable complexes that are effectively recognised by the CD4+ T-lymphocytes [30–34]. In genetically predisposed subjects expressing HLA-DQ2/DQ8, these peptides are capable of stimulating specific CD4+ cells which secrete interferon gamma (IFN-γ) (T helper 1 response) and activate different signalling pathways, leading to the alteration of the mucosae (lymphocytic mucosal infiltration with IELs, villous atrophy [VA], crypt hyperplasia) [4,35–37]. This process consists in a veritable communication between different cellular populations, including the intraepithelial lymphocytes (IELs), which are cytotoxic CD3+/CD8+ lymphocytes (B+ granzyme and TIA1+) found in very high number in the intestinal epithelium of patients with CD, the intestinal epithelial cells (IECs), the dendritic cells and the macrophages. Interleukin 15 (IL-15) plays a major role in these cellular interactions. IL-15 is greatly increased in the mucosa of patients with CD and acts not only on a physiological level in the development, differentiation and function of the intestinal IELs, NK and NKT cells, but also in the disease process since it increases the cytotoxic activity of the IELs and the expression of the cytotoxic IEL ligands on the IECs surface, such as MICA [38]. In addition, CD is associated with the secretion of autoantibodies (AB) (anti-endomysial, anti-transglutaminase and anti-gliadin) used for diagnosis and follow-up.

The complications of CD are now better understood, both from the diagnostic and the pathophysiological points of view. RCD is a form of CD that is resistant to gluten-free diet (GFD) and comprises two types. Type 1 RCD (RCD1) mimics CD in all respects except for the probable autonomisation of inflammatory mechanisms initially induced by gluten-derived gliadin, which could explain the resistance to the GFD. Type 2 RCD (RCD2) is defined by the emergence of a population of abnormal IELs within the epithelium, which is characterised by a clonal rearrangement of the TCR gamma (TCR-γ) and very stereotypical phenotype anomalies including the absence of surface expression of the CD3-TCR complex and generally of the CD8 co-receptor, contrasting with the intracytoplasmic presence of the CD3ζ molecule. This thus suggests an equivalent of intraepithelial T lymphoma known as low-grade [4,39,40]. Indeed, although the cytological appearance is normal and the absence of active in situ proliferation, the presence of clonal rearrangements of the TCR-γ, sometimes also chromosomal anomalies, as well as their potential dissemination in the chorion, blood or other extra-intestinal sites such as the skin and lung, are all highly suggestive factors of their malignant nature [4,16].

IL-15 again plays an essential role here [38,41]. It induces a pro-inflammatory response by interfering with the anti-inflammatory signals that are normally activated by transforming growth factor beta-1 (TGF-β1) [42]. This signalling inhibition by TGF-β1 in the T-lymphocytes by IL-15 is mediated by c-jun N-terminal kinase (JNK) activation, which antagonizes activation of the Smad2, 3, 4 complex induced by TGF-β1 [43]. This results in an increased secretion of pro-inflammatory cytokines, T-cell proliferation and cytotoxicity [38,44]. IL-15 might also contribute to apoptosis deregulation, thus promoting the emergence of an aberrant T-cell clone, but this hypothesis is still under investigation.

At the end of the 1990s, several authors showed that RCD2 could be the intermediary link in the progressive continuum of CD to EATL [4,39,40,45]. In fact, from the immunophenotypic point of view, the aberrant clonal intraepithelial T-cell population in RCD2 presents the
same clonal rearrangement of the TCRγ as that of EATL [4,26,46,47]. Moreover, the intraepithelial origin of EATL is confirmed by the expression of CD103, like the abnormal IELs of RCD2 but can be distinguished by its high proliferation index (Ki67+) and frequent CD30+ staining. This continuum involves genetic reprogramming and phenotype alterations of the IELs, which are responsible in the first place for tissue damage relative to the resistant CD, and then on their uncontrolled growth and eventual transformation into EATL [4,39].

Finally, molecular events contribute to the growth and clonal transformation of the IELs from the early stage of RCD with the frequent presence of a trisomy 1q24-q44, which is found recurrently in over 90% of RCD cases. This trisomy 1q24-q44, which was first detected in IEL lineages from intestinal biopsies of patients with RCD2 or in circulating abnormal lymphocytes when present in excess [48], was also found in 75% of type I EATL cases [10,49–51]. In a more advanced stage, there appears to be other recurrent anomalies in the type I EATL, including in particular a chromosomal gain in 9q33 (found in 70% of cases), losses of the 16 and a loss of 9p21 heterozygosis [10,49–51]. These molecular data reinforce the relationship between RCD2 and EATL.

Presentation and diagnostic management of enteropathy-associated T-cell lymphoma

The clinical and/or histological diagnosis of CD is not always made before that of EATL, since depending on the series, which are of course heterogeneous, it is known before the management of EATL in 20 to 100% of cases (in these cases, there is certainly a selection bias related to the recruitment centre) [11–14]. This data confirms the now very common belief that there is a high prevalence of undiagnosed CD (1/300) in the general population compared to that of diagnosed CD (prevalence of 1/3000) [35]. The discovery therefore that CD can be accompanied from the beginning by RCD2, the lesional equivalent of low-grade intestinal lymphoma, and/or EATL, especially in the absence of improvement and/or in the event of worsening despite several months (>12 months) of well-conducted GFD [4]. Conversely, the discovery of intestinal T-cell NHL requires that underlying CD be ruled out by appropriate methods (CD serology testing, duodenal biopsies with quantitative evaluation and immunophenotyping of IELs [52], HLA typing, investigation of T-cell clonality) and especially that the nutritional impact be evaluated.

It is important to note that EATL is a complication of adult CD or RCD but has not been observed in children; the youngest age in which the diagnosis of RCD2 has been made is 25 years. The suggested reasons are that the diagnosis of CD is more difficult in adults than in children and that the duration of antigenic stimulation is in fact much greater. Malamut et al. also showed that advanced age is an independent risk factor of EATL occurrence, independent of the type of possible associated RCD [16]. These data suggest that prolonged inflammation over many years promotes the emergence of a clone, followed by its persistence and spread (see above).

The relative risk (RR) of NHL was initially estimated at 80 in the absence of a strict GFD, but for all celiac patients, this RR, after having been overestimated, was reported to be 6 compared to the general population [9,53]. The expected incidence of EATL in the celiac population relative to the general population is estimated between 0.22 and 1.9 patients per 100,000 persons per year in Europe [9,54–56]. The prevalence of T-cell NHL in CD is difficult to know exactly and seems low, well beneath figures quoted in older publications (<5% of adult CD) [57]. Finally, when CD has been diagnosed beforehand, the mean time to the occurrence of EATL is about 10 years [57,58].

The median age of occurrence is 59 years [11,14,59]. The initial clinical presentation is not specific since it can appear like the classical symptoms of CD. However, resurgence or exacerbation of these symptoms in case of previously diagnosed CD that have been correctly and effectively treated until then with a strict GFD should raise suspicions of EATL. The symptoms consist foremost of abdominal pain of all kinds (65–100%) and weight loss (50–80%), plus diarrhoea more rarely (40–70%) [4,11–14,59]. A complication signalling the diagnosis is not rare (<40% and up to 70% depending on the series) and may require initial emergency therapeutic surgical intervention [4,12,59]. GI perforation (25–50%) is the most prominent of these complications; GI haemorrhage occurs most often in the course of CT but can be a signalling symptom for the diagnosis; and intestinal occlusion with an insidious and even chronic presentation is more rare but contributes to digestive tolerance and nutritional problems [11–14,60]. Undernourishment is in fact a very common problem, especially if the EATL occurs associated with type 1 or 2 RCD, and contributes to the poor tolerance and delay of curative treatment (delay of postoperative healing, increased CT toxicity due to hypoalbuminaemia with diarrhoea and exacerbated mucositis, more frequent and severe infections) [4]. The general health status is very often altered early with a performance status (PS) rating of 2 at the time of treatment as a general rule. The signs of clinical progression (or B symptoms = fever, night sweats), other than weight loss, are however only present in less than one third of cases [11–13].

Biological abnormalities are also non-specific and, except for hypoalbuminaemia (<25 g/l) which exists in nearly all patients (85%), are rarely seen and are not very significant: anaemia (<65%), lymphopaenia (40%) and increased LDH in only 25% of cases [11,59].

The diagnostic studies primarily include: abdominal computed tomography scan (CTS) to rule out small bowel tumours, mesenteric adenopathies, extra-digestive lesions and potential complications such as perforation or intestinal occlusion; upper GI endoscopy with multiple systemic biopsies for lesional work-up of the CD ± RCD and EATL if it is accessible. These are greatly enhanced with the emergence of new diagnostic tools: computed tomography enteroclysis [61]; double balloon enteroscopy, either upper or lower, especially useful for the exploration and biopsies of the distal small bowel, thus avoiding exploratory laparotomy for histological diagnosis when the lesion can not be reached by standard GI endoscopy [62,63]; positron emission tomography with CT scan (PET-CT scan) is very promising, despite the usual artefacts of the digestive tube, and appears to be superior to simple CT scan for detection of NHL due to the significantly higher standard uptake value (SUV), especially compared to potentially much weaker signals emitted by
RCD and CD which exhibits little or no uptake [64,65]; lastly, capsule endoscopy (CE) is an overall test for lesions of the digestive tube and can be used to orient endoscopy and/or surgery for biopsies [66,67]. It should be avoided however if there is suspicion of GI stenosis, as passage of the capsule can be blocked.

Following these examinations, it appears that involvement of the small bowel is usually multifocal (30–100% according to the series) and primarily affects the jejunum (70%) and proximal ileum [12,14,59]. Likewise, the disease has often spread to stage III/IV by the time the diagnosis is made (40–60% of cases); extra-small bowel (colon, stomach) and extra-GI (skin, bone marrow, lungs, neuromeningeal) spread must therefore be systematically investigated through appropriate examinations, as well as a leukemic phase of the disease with immunophenotyping investigations of the blood and molecular laboratory testing of a circulating tumour T-cell clone [14].

**Histology**

CD, RCD, ulcerative jejunitis and EATL can coexist in a single patient. Histological assessment of each of these diseases is mandatory for adapting the therapeutic management of each one (thus, the recent data suggesting aggressive treatment of RCD2 with conventional polychemotherapy [68], see “Future perspectives” chapter below) and also has prognostic value. A re-evaluation of the underlying enteropathy when known beforehand is necessary, even more so since poor control can result from the lack of a GFD and/or development of RCD which is unresponsive to diet. In addition, as noted previously, underlying enteropathy is not always known, thus requiring that it be ruled out in all cases of T-cell NHL of the small bowel.

**Celiac disease**

CD must be assessed objectively at a distance from the tumour zone, since there are areas of VA on the periphery and/or infiltration by the IELs, but that is not sufficient for a diagnosis of CD [59]. This diagnosis is classically defined as the presence of a variable quantity of VA in the proximal intestine, usually subtotal to total, in association with hyperplasia of the crypts and classic excess infiltration of the epithelium by IELs but with normal CD3+, CD8+ and CD103+ phenotype (integrin αEβ7, whose ligand is E-cadherin) [26].

**Refractory celiac disease of type 1**

The histological lesions of RCD1 are identical to those of CD, including IELs with normal phenotype, but they do not resolve with a GFD that is well-conducted over a 12-month period [4,16].

**Refractory celiac disease of type 2**

RCD2 is now recognised as a genuine small cell intraepithelial T-cell NHL and readily presents in the form of ulcerative jejunitis on endoscopy [4]. It is characterised by an increased number of IELs, which, although retaining normal morphology, present with abnormal phenotype and clonal rearrangement of the TCRγ; these are found fairly consistently (80%), evidencing the clonal character of the enteropathy [4,39,40,45,69]. The phenotype study can be attained through standard immunohistochemistry techniques on slices that can be done retrospectively and be refined and/or confirmed through techniques of cellular isolation on fresh samples and immunostaining using flow cytometry (FACS), which is currently only available in specialized centres. The abnormal phenotype of IELs signifies an absence of the surface expression of the TCR-CD3 complex [4,39,40,45,69]. This phenotype, usually surface CD3 (sCD3)−, intracytoplasmic CD3 (iCD3)+, CD8−, CD103+, TCR−, provides proof of the probable blockage, more or less late, of T-lymphocyte differentiation; there are studies underway to clarify the stage. In addition a recurrent trisomy 1q was found, justifying systematic karyotyping at the initial evaluation if the patients have abnormal cells circulating in the blood; karyotyping on IELs requires an available lineage, which is not routinely possible [48]. This anomaly can also now be detected by fluorescence in situ hybridization (FISH) analysis.

**Enteropathy-associated T-cell lymphoma (EATL)**

EATL (which is subtype I in the latest WHO classification [2]) is a T-cell NHL that is usually large cell, known as 'high-grade', both in its clinical and histological presentation. It consists of a massive tumour infiltration, usually transepithelial, which causes GI stenosis and perforation. Macroscopically these are seen as ulcerations, infiltration and induration of the wall and/or nodules. Several histological varieties are usually reported, but most cases consist of medium- to large-sized cells with a pleomorphic appearance (58%) and an increased mitotic index [11,59,70]. They often occur with a contingent of polymorphic reactive cells of varying intensity, including small lymphocytes, histiocytes and polynuclear cells, especially eosinophils or even epithelioid granulomas. Among the other features, we can cite the possibility of infiltration by cells with an immunoblastic or anaplastic appearance, matched in this case to CD30 positivity but to anaplastic lymphoma kinase (ALK) negativity. One main characteristic which cannot be ignored and which reflects the origin of the tumour from IELs is the very significant epitheliotropism of the tumour cells on the surface epithelium and glands [59]. The tumour phenotype is usually sCD3−, iCD3+, CD4+, CD8−, CD103+, TCR−, CD30±, CD5+, CD80−, CD56−. Immunostaining is possible; CD4+ is more rare. The tumour cells are cytotoxic and express the classic markers TIA1, granzyme B and perforin, like their biological equivalent, the IELs [4,23,26,27,59,71].

In rare cases of EATL, which are currently classified as subtype II, the morphological and phenotypic appearance is more stereotypical and is characterised by monomorphic proliferation of small- to medium-sized CD3+ CD8+ TCRβ+ and expressing CD56. The presence of CD56 raises the possibility of a different lymphomagenic pathway and its connection with the rare NK/T-cell type NHL of the intestine. These CD56+ NHL are associated with an enteropathy in significantly fewer instances (44%) and have no proven link with CD [59,72,73]. A recent study combining comparative genomic
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hybridization and an HLA-DQB1 genotype study confirmed that type II EATL is a distinct form of lymphoma complicating CD. In fact, 47% of cases are not associated with the HLA-DQ2/DQ8 genotype (consistent in CD) and 50% of cases exhibit no signs of enteropathy on the adjacent mucosa. Lastly, there are distinct molecular anomalies (rare 1q gain, frequent gain of the MYC locus), in keeping with a distinct lymphomagenic pathway from the classic type I EATL [10].

Therapeutic management

In order to better appreciate the intrinsic methodological quality of the different therapeutic clinical studies cited in this review, we assessed their level of proof in accordance with evidence-based medicine (EBM) criteria. Each study was thus assigned a grade of recommendations (grades A to E) as defined in Table 1 [74].

To this day there is still no validated or consensual treatment for EATL. This is due on one hand to its extreme rarity (less than 1% of NHL cases, about 20% of GI NHL cases) [3] and on the other to the lack of ‘‘homogenous’’ (grade B) cohort studies and finally to the lack of significant efficacy of therapeutic strategies used until now.

As EATL is a rare disease in which there is no standardised treatment, there was no justification up until now to carry out randomised placebo-controlled therapeutic clinical studies (grade A). In addition, even when non-randomised, prospective studies are rare. Retrospective studies have included only very small cohorts (grade D) and their results are often contradictory. This is due probably in part to the wide heterogeneity of the cohorts of patients with EATL with regard to age, stage, complications, type of CT, therapeutic line, previous history of surgery, history of radiotherapy use, etc. Lastly, the many published ‘‘clinical cases’’ (grade E) also lend a bias to the results by reporting rare and non-reproducible clinical situations. EATL is often studied within vast cohorts of peripheral T-cell lymphomas (PTCL) or GI NHL, in which they are in the minority thus preventing the generalisation of their results. Moreover, although it still needs to be demonstrated through statistical studies, the prognosis of EATL appears to be markedly worse than that of PTCL. Therefore the results of these studies are not valid for this minority sub-group of patients.

Surgery

Initial surgery still seems to be very commonly practiced today (up to 70% of cases depending on the series [11,13,14,76]). It is usually done on an emergency basis for diagnostic purposes when endoscopy is not possible and/or to treat one or several complications (45 to 72% of surgical interventions, depending on the series [11–14,60,77]). Over 50% of patients are thus diagnosed based on a surgical complication that reveals the disease. This reduces their survival significantly compared to elective surgery [12]. The benefit of surgery is in fact very questionable since some studies report better survival results when CT is combined with an initial maximum tumour resection [12,77,78]. Surgery alone is not however therapeutic in the management of NHL; its use delays the initiation of CT and the underlying undernutrition exposes the patient to problems of healing and infection. The key point therefore is that it must never be used to the exclusion of other treatments, especially CT. The question of the use of initial surgery for preventing complications (perforation, haemorrhage, fistula) or for so-called ‘‘cleansing’’ surgery therefore remains open since no randomised studies have been performed until now.

Radiotherapy

There is very little data in the literature that illustrate the effects of radiotherapy in the treatment of EATL. In the prospective study of the German Study Group (grade B), it was systematically recommended for stages III/IV but could never be provided since 85% of the selected patients died early [12]. In another study, radiochemotherapy was considered to be the best therapeutic combination for localised stages. Among the eligible patients in this study for radiotherapy, all of those that were not in complete remission (CR) after CT became so after radiotherapy [13]. In fact, the benefits of radiotherapy remain largely questionable. On one hand, it is no longer recommended in GI B-cell NHL because it has no prognostic impact on a survival that is already excellent (cumulative 2-year survival of 94%); on the other hand, it exposes the patient to acute and/or chronic complications of small bowel irradiation. Our opinion is that it probably has no role in the curative treatment of EATL but remains a subject of interest. Once again, the lack of randomised studies does not enable a definitive conclusion to be drawn with regard to its potential benefits.

Chemotherapy

Though there are many CT protocols described in the literature, until now none of them has been able to distinguish itself from the others in providing a significant and reproducible benefit. In addition, they consist of small cohorts, which are essentially retrospective and single-centred with inhomogenous therapeutic regimens, disappointing and contradictory results and a prognosis that is very often poor. They are listed in Table 2 [11–14,60,75,76,79–81] with the details of each CT protocol described in the legend. Excluding the clinical cases, we then summarised the key points of these studies.

CT is only practicable for the diagnosis in three-quarter of patients (66 to 77% according to the series). In fact, 30% never receive it due to their poor general health status and early death from complications (first 3 months). In addition, among patients that are able to receive initial CT, an average of 50% are unable to finish their therapeutic programme.

Regardless of whether initial surgery is performed, CR is only obtained in 35 to 40% of patients treated with CT, with the overall response rate being 40 to 60% according to the series. CR is most often achieved in patients with stage I/II: 50 to 80% CR in the best published series (although grade D) [13] versus (vs.) 0 to 11% for stages III/IV. The median duration of CR (or relapse-free survival [RFS]) does not differ significantly however between stages I/II vs. III/IV (5.3 vs. 5.8 months). A single series (grade B) distinguished itself by a post-CT median RFS of 28 months (range: 17–39), although unfortunately non-reproducible [12]. In fact, close to 80% of patient responders relapse after a median period of 6
months (range: 1—60), which is equivalent to a 1- and 5-year RFS rate of 19.4% and 3.2%, respectively [11—14,75].

Less than half of patients respond to salvage therapy, and only a rare number can benefit from several therapeutic lines.

80 to 85% of patients die from disease progression and/or complications, with an estimated median survival of 6 to 7.5 months (range: 0—83) and no significant difference between the stages [11—13]. However, according to the only multicentre, prospective study from the German Study Group (grade B) [12], 38% of patients with stage I/II will be alive in two years (range: 17—59) vs. only 14% of those with stage III/IV (range: 0—32); although here again, this difference is not statistically significant in this study.

The CHOP protocol (combination of doxorubicin—cyclophosphamide—vincristine—prednisone), which is the most widely recognised, should probably no longer be recommended as a standard treatment of EATL [11—14,75]. In fact, the combined analysis of different studies published up to now show that the overall median survival post-CHOP therapy is only 7 months (thus equivalent to that of other chemotherapies) and the cumulative survival at 2 years post-CHOP, regardless of the stage, is 28% (range: 13—43%). This poor result was even truer in stages III/IV in which there was no significant survival difference with or without CHOP, since the cumulative survival at 2 years was 20% with CHOP vs. 11% without CHOP [12]. It seems that the CHOP protocol may only benefit stages I/II, with a better cumulative 2-year survival with CHOP of 49% vs. 14% without CHOP [12]. It should be noted that a dose-escalated CHOP protocol with the addition of etoposide (CHOEP) provides no therapeutic benefit and has greater haematological toxic effects [79].

Despite these poor results, there are always one or two patients in each series that stand out with very encouraging prolonged relapse-free survival (range: 49—219 months) [11]. However, no particular clinical, histological and/or therapeutic characteristics differentiate them from other patients, although there are presently no studies available specifically analysing the prognostic factors of the disease.

In general, CT should be systematically planned for all patients, but the results of current protocols remain disappointing with a cumulative 1-year survival of 33 to 38.7% and 5-year survival of 9 to 19.7% according to the series [11,12,14]. It is therefore necessary to find new combinations of CT that are more effective, particularly for stages III/IV.

### High-dose chemotherapy with autologous peripheral blood stem cell transplantation (auto-PBSCT)

The benefits of auto-PBSCT are controversial. On one hand, this procedure is rarely feasible since at this time most of the patients (more than 50%) are not able to have the auto-PBSCT procedure for previously cited reasons of non-response, early breakthrough, toxicity and complications. On the other hand, the results are mixed and even contradictory. Two examples will illustrate this topic, along with a summary table (Table 3) [11,68,72,76,77,82—86]. The first example supports such a procedure and was reported by Bishton and Haynes (grade E study) [81,82]. It used an IVE regimen (combination of ifosfamide, etoposide and epirubicin) × 2, followed by high-dose methotrexate (HD MTX) × 2, then autologous transplantation after BEAM conditioning regimen (combination of carmustine, cytarabine, etoposide, and melphalan).

### Results

Five of the six CR, in which four of the five were prolonged [1.8—4.3 years] and one out of six very good partial responses (PR) were observed. These good results however are tempered by the fact that this study was based exclusively on localized stage I (5/6) and II (1/6) disease. The other example, which did not support this procedure, was reported by Al-Toma et al. [77]; it was based, on the contrary, on four patients that all had advanced stage III and IV disease treated with CHOP (one patient switched at 12 months to DHAP/VIM), followed by high-dose CT with melphalan and fludarabine or BEAM and then auto-PBSCT (grade D study). In this series, three-quarter of the patients died between 2 and 9 months and only one prolonged CR was observed at 32 months. It is difficult to draw definitive conclusions from such small numbers of patients. It seems fairly clear however that the dose intensity effect is probably only of benefit in the localised stages of the disease.

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**Table 1** Level of proof of treatment trials according to Sackett et al. [74].

<table>
<thead>
<tr>
<th>Types of study and grade of recommendations</th>
<th>Grade A</th>
<th>Grade B</th>
<th>Grade C</th>
<th>Grade D</th>
<th>Grade E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review of randomized controlled trials (with homogeneity) OR single randomized controlled trials (with narrow CI) OR situation where treatment led to obvious improvement (all or none)</td>
<td>Systematic review of cohort studies (with homogeneity) OR single cohort studies (including low-quality randomized controlled studies) OR outcome study</td>
<td>Systematic review of case-control studies (with homogeneity) OR single case-control study</td>
<td>Series of cases OR cohort studies OR low-quality case-control</td>
<td>Expert opinions</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval.
<table>
<thead>
<tr>
<th>Authors [references]</th>
<th>Type of study/grade of recommendation</th>
<th>Number of patients</th>
<th>Stage</th>
<th>Surgery</th>
<th>% CT</th>
<th>Types of CT</th>
<th>Response</th>
<th>Overall survival (OS)</th>
<th>Relapse-free survival (RFS)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egan et al. [14]</td>
<td>Retrospective (1972—1994) Monocentric Grade D</td>
<td>31 B or T-cell NHL 24 EATL</td>
<td>I—II 2/3 III—IV 1/3</td>
<td>51%</td>
<td>45 CHOP ProMACE-MOPPBACOP</td>
<td>NR</td>
<td>1 and 5 yrs OS: 31 and 11% Median survival: 10 months (0—196)</td>
<td>NR</td>
<td>1/3 inapt for treatment (n = 11 including 8 post-mortem diagnosis) Survival without CT &lt;3 months</td>
<td></td>
</tr>
<tr>
<td>Gale et al. [11]</td>
<td>Retrospective (1979—1996) Monocentric Grade D</td>
<td>31 EATL</td>
<td>I—II 1/3 III—IV 2/3</td>
<td>80%, n = 25 (13 in ES)</td>
<td>77 VAMP, n = 5 CHOP, n = 13 PEACE—BOM, n = 3</td>
<td>OR 58% CR, n = 10 PR, n = 4</td>
<td>1 and 5 yrs OS: 38.7 and 19.7% Median survival: 7.5 months (0—83)</td>
<td>1 and 5 yrs RFS: 19.4 and 3.2%</td>
<td>50% premature treatment interruption due to progression and/or complications 79% relapse within a median time of 6 months (1—60) 84% death of PD and/or complications</td>
<td></td>
</tr>
<tr>
<td>Daum et al. [12]</td>
<td>Prospective (1995—1999) Multicentric Grade B</td>
<td>35 intestinal T-cell NHL 80% EATL</td>
<td>I—II 60% III—IV 40%</td>
<td>Always proposed (45% in ES)</td>
<td>66 CHOP × 6</td>
<td>35% CR (0% of st III—IV, 50% of st I—I)</td>
<td>Median survival at 2 yrs: 28% (13—43%)</td>
<td>Post-CT RFS = 28 months (17—39)</td>
<td>1/3 inapt for CT ⇔ 29% early death (&lt;3 months) CHOP benefited only to st I—I No difference in survival depending on the st (I—I 38% vs. III—IV 14%) Emergency vs. planned surgery impaired prognosis</td>
<td></td>
</tr>
<tr>
<td>Wöhrer et al. [79]</td>
<td>Prospective (2000—2003) Monocentric Grade D</td>
<td>10 intestinal T-cell NHL 4 EATL</td>
<td>I—II 60% III—IV 40%</td>
<td>NR in about 50%, the others in ES</td>
<td>100 CHOEP</td>
<td>CR, n = 3 PR, n = 3 PD, n = 4</td>
<td>Median survival: 7 months (2—16)</td>
<td>NR</td>
<td>No benefit of the CHOP More haematological toxicity</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 (Continued)

<table>
<thead>
<tr>
<th>Authors [references]</th>
<th>Number of patients</th>
<th>Stage</th>
<th>Surgery</th>
<th>% CT</th>
<th>Types of CT</th>
<th>Response</th>
<th>Overall survival (OS)</th>
<th>Relapse-free survival (RFS)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novakovic et al. [13]</td>
<td>Retrospective Monocentric Grade D</td>
<td>15 intestinal T-cell NHL 67% EATL (n = 10)</td>
<td>I–II 40% III–IV 60%</td>
<td>n = 11 (&gt;50% in ES)</td>
<td>100 CHOP, n = 13 Others, n = 2</td>
<td>CR 40% SD 20% PD 40%</td>
<td>1 and 5 yrs OS: 33 and 9% Median survival: 6 months (1–27)</td>
<td>Post-CT RFS = 5.3 months (2–12)</td>
<td>50% premature treatment interruption 87% death of progression and/or complications</td>
</tr>
<tr>
<td>Yin et al. [60]</td>
<td>Retrospective Monocentric Grade D</td>
<td>7 intestinal T-cell NHL</td>
<td>I–II 30% III–IV 70%</td>
<td>71% (43% in ES)</td>
<td>57 CHOP</td>
<td>NR</td>
<td>NR</td>
<td>Apparent median survival &lt;7 months</td>
<td></td>
</tr>
<tr>
<td>Sieniawski et al. [76]</td>
<td>Prospective Multicentric Grade B</td>
<td>54 EATL</td>
<td>IE 15% IIE 67% IV 17%</td>
<td>91%</td>
<td>65 CHOP-like</td>
<td>NR</td>
<td>5 yrs OS: 22% Median survival: 7 months</td>
<td>5 yrs RFS: 20% Median RFS: 3.4 months</td>
<td>35% never received CT ⇔ early death 44/54 including deaths</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors [references]</th>
<th>Grade of recommendation</th>
<th>Nb of EATL</th>
<th>Nb of patients with auto-PBSCT</th>
<th>Stage</th>
<th>Initial chemotherapy</th>
<th>Pre-graft conditioning</th>
<th>Response/Overall survival (OS)/Progression-free survival (PFS)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gale et al. [11]</td>
<td>Grade D</td>
<td>31</td>
<td>2</td>
<td>NR</td>
<td>PEACE-BOM</td>
<td>BEAM</td>
<td>1 death at 69 months of progression 1 CR stable at 64 months</td>
<td>Salvage situation in both cases</td>
</tr>
<tr>
<td>Okuda et al. [72]</td>
<td>Grade D</td>
<td>1</td>
<td>1</td>
<td>NR</td>
<td>CHOP × 8 then ESHAP (relapse)</td>
<td>MCVC</td>
<td>Death at 8 months of intestinal and CNS relapse CR at 18 months (last follow-up)</td>
<td></td>
</tr>
<tr>
<td>Rongey et al. [83]</td>
<td>Grade D</td>
<td>1</td>
<td>1</td>
<td>IIE</td>
<td>CDE × 4 then CHOP × 3</td>
<td>BEAM</td>
<td>CR at 18 months (last follow-up) Majority of localised stages Initial surgery in 4/5</td>
<td></td>
</tr>
<tr>
<td>Jantunen et al. [85]</td>
<td>Grade E</td>
<td>5</td>
<td>5</td>
<td>IE, n = 3</td>
<td>IIE, n = 1</td>
<td>IV, n = 1</td>
<td>CHOP</td>
<td>BEAC, n = 3 BEAM, n = 2 Median survival = 2 months 2 early deaths of toxicity 3/3 relapses (0—14 months)</td>
</tr>
<tr>
<td>Blystad et al. [86]</td>
<td>Grade D</td>
<td>2 among 40 T-cell NHL</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Majority of PTCLu and anaplastic NHL</td>
</tr>
<tr>
<td>Bishton and Haynes [82]</td>
<td>Grade D</td>
<td>6</td>
<td>6</td>
<td>IE, n = 5</td>
<td>IIE, n = 1</td>
<td>IVE × 2 then HD MTX × 2</td>
<td>BEAM</td>
<td>CR, n = 5 VGPR, n = 1 4 prolonged CR (1.8—4.3 yrs) Localised stage of the disease may explain good results</td>
</tr>
<tr>
<td>Reimer et al. [84]</td>
<td>Grade B</td>
<td>5 among 83 T-cell NHL</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Majority of PTCLu and anaplastic NHL</td>
</tr>
<tr>
<td>Al-Toma et al. [77]</td>
<td>Grade D</td>
<td>4</td>
<td>4</td>
<td>III, n = 3</td>
<td>IV, n = 1</td>
<td>CHOP, n = 4 (+αCD52, n = 1) DHAP/VIM for salvage, n = 1</td>
<td>MLP-Fluda, n = 2 BEAM, n = 2</td>
<td>3/4 deaths of relapse (2—9 months) 1 CR stable at 32 months CR: 72% OS at 5 yrs: 67% RFS at 5 yrs: 56% Disseminated stage of the disease may explain poor results</td>
</tr>
<tr>
<td>Sieniawski et al. [76]</td>
<td>Grade B</td>
<td>72 including 18 planned for auto-PBSCT</td>
<td>12 among the 18 planned</td>
<td>IE 22 %</td>
<td>IIE 56 %</td>
<td>IV 22 %</td>
<td>CHOP × 1 then alternating IVE/ID MTX × 3</td>
<td>NR</td>
</tr>
</tbody>
</table>

or in patients in CR. It is therefore important to continue to explore high-dose CT with auto-PBSCT in order to better define the indications and toxicity, even if it seems acceptable in patients in CR [77,82,85,86].

Immunotherapy

There is very little data in the international literature describing the potential benefits of monoclonal AB, at the forefront of which is alemtuzumab (targeting CD52), and of allogeneic bone marrow transplantation. The role of anti-CD52 monoclonal AB has still not been completely defined in a broad sense within the therapeutic choices of malignant T-cell blood diseases [87] and its infectious risks prevent its use in already very debilitated patients. The combination with gemcitabine was very recently reported as being effective in one case of EATL [88].

With regard to allogeneic bone marrow transplantation, there are no cases or homogeneous cohorts available in the international literature clearly describing its effect. This type of procedure however has true future potential (see "Future perspectives" chapter below) in this disease due to its CT resistance. Additionally, it is now possible to administer attenuated conditioning, which is preferable in these patients who are particularly susceptible to the toxic and infectious complications of CT.

The principles of treatment

The following observations can be made from these data.

Curative treatment

Curative treatment can include several facets, the main one being CT. Initial surgery, as previously described, is, in our opinion, either diagnostic or reserved for the management of initial complications, which usually occur on an emergency basis. It can also be used for the prevention of early complications but this indication needs to be validated. CT should be administered systematically and early, whether or not surgery is performed beforehand, with protocol(s) still to be defined (see below). It should include systematic neuromeningeal prophylaxis via intrathecal CT. Lastly, radiotherapy is not indicated due to its toxicity and the lack of proof of its efficacy.

In all cases, very close monitoring of the therapeutic response (CT scan; GI endoscopy; PET-CT, the role of which remains to be better defined) will be essential for early detection of non-response or poor response to CT and/or complications. An evaluation after a first course and then every two courses does not seem excessive to us, given the frequency of primary failures and secondary breakthroughs, the rapid disease progression of some patients, the inherent risks of extra-digestive tumour dissemination (especially meningeal) and the benefits of very early change in the line of CT.

Management

The management of the underlying enteropathy should be maintained or initiated (when the enteropathy was unknown prior to the EATL) with strict follow-up. The GFD is imperative for fighting against malabsorption and maintaining the most satisfactory nutritional state possible. The response to the diet will be monitored with nutritional markers, celiac serology testing and GI endoscopy with systematic biopsies.

The GFD should be maintained even if the disease progresses to RCD, which is characterised by resistance to the GFD. In this case, it is not known whether continued exposure to gluten will promote progression to EATL. Questions can also be raised as to its direct prognostic effect in the response to treatment of EATL, as well as its possible role in the prevention of relapses. The RCD will once more be monitored by GI endoscopy with routine biopsies and ideally quantification and phenotyping of the IELs by flow cytometry.

RCD2 poses particular problems for management due to its often major impact on nutritional status, leading to the development of progressive cachexia in some patients or even death. Malamut et al. [16] reported a clinical response rate to corticosteroids of about 90 and 76% in cases of RCD1 and RCD2, respectively, but also 80% corticosteroid independence. The other immunosuppressant drugs are reputed to not be very effective, but rare patients can show improvement. These drugs include: methotrexate, ciclosporin, azathioprine and anti-tumour necrosis factor alpha (TNF-α). The exact effect of CT on RCD is not known. Fludarabine, imatinib and CHOP CT appear to be ineffective. Conversely, cladribine and alemtuzumab were reportedly effective in four patients with clinical and histological improvement, but three-quarter developed very early EATL, suggesting either a promoter effect of these treatments on lymphomagenesis or the pre-existence of EATL even before their initiation [16]. Finally, high-dose CT procedures with auto-PBSCT are currently under study [68]. The preliminary results have demonstrated the feasibility of this procedure, especially with regard to toxicity, but the long-term benefits have yet to be clarified. In practice, in the event of a combination of EATL and RCD, it is always essential to accurately assess the effect on the RCD of the CT recommended for EATL; the same applies with the possible use of monoclonal AB.

Symptomatic treatment

Symptomatic treatment is also fundamental, as patients are likely to die from the associated complications as from the NHL itself. This consists of:

- enteral and/or parenteral nutritional support at the least sign of deficiency, a nearly constant condition, with the implementation of home care;
- close monitoring and early management of different possible complications:
  - infectious (routine prescription for granulocyte colony-stimulating factor [GCSF], for cytotoxic CT and early antibiotic treatment of GI bacterial translocations since this is the main entry point of infections),
  - undernutrition (prevention and care of decubitus ulcers, treatment of osteoporosis, vitamin supplementation),
  - GI (mucositis, diarrhoea, perforation, haemorrhage, etc.).

Whether the treatment is curative or symptomatic, multidisciplinary and collaborative management between the
haematology, gastroenterology and visceral surgery departments at any time during treatment is essential to ensure the proper care relative to the complications.

Future perspectives

There are many future prospects in light of the considerable improvement that can be made in the prognosis of EATL. First of all, the overall management can be optimised; in particular, the role of surgery may be defined and CT protocols improved in terms of efficacy primarily and toxicity secondarily. New protocols must be validated through patient cohort studies which are prospective, multicentric and collaborative, since randomised studies still appear to be difficult to perform at this time. The aim of the INCa Lymphoceliac project is thus to harmonise the therapeutic strategies on a national level and to propose protocols for prospective therapeutic clinical studies and perhaps then participate in international studies.

New chemotherapy combinations and/or an ongoing administration

New CT combinations and/or an ongoing administration could increase the efficacy/toxicity ratio. This type of administration seems to be more effective on small cell variants of T-cell lymphocytic proliferations, as was suggested in mycosis fungoides [89,90], which raises the hypothesis of possible efficacy on RCD2. The CDE protocol (combination of continuous cyclophosphamide, doxorubicin and etoposide over 4 days) is thus being evaluated prospectively in our centre. The Hyper-CVAD protocol (alternation of doxorubicin, cyclophosphamide, vincristine, prednisolone/aracytin, methotrexate) also needs to be investigated more closely, since it resulted in a 34-month CR in one patient [80] (expert opinion), but its considerable toxicity must be balanced with its efficacy. Consequently, it could be offered to patients with a good initial response or after surgery. Other protocols have even more potential however. The recent Scottish experiment (grade B study) is encouraging consisting in four to six courses of an alternating regimen of IVE (ifosfamide—etoposide—epirubicin) and intermediate doses of methotrexate, followed by high-dose CT with auto-PBSCT. The results that were recently presented at the 2008 American Society of Hematology (ASH) conference were very positive [76]. Sixty-seven percent, i.e., 12/18, of patients scheduled to receive an auto-PBSCT were able to receive it. Compared to a historical control group treated according to a CHOP-like type of design, the complete response rate was 72% vs. 42%, progression-free survival (PFS) was 56% vs. 20% and overall 5-year survival was 67% vs. 22%, respectively. These particularly favourable results justify being validated prospectively and in larger cohorts. They suggest not only the benefit of this new combination of CT (IVE/MTX) but also support that of high-dose CT for consolidating the obtained response.

The use of monoclonal antibodies

AB that target CD52 (alemtuzumab, MabCampath®), combined with CT (CHOP—Campath for example) intervene by sensitising tumour cells to the CT and by contributing to the treatment of the underlying small cell lymphoproliferation [87]. However their use is tempered by disappointing results in the only two reported cases, in which one patient developed EATL while receiving a CD52-targeting AB, suggesting either the pre-existence of EATL and the ineffectiveness of MabCampath®, or an inducer effect [16,91]. AB targeting CD30, the use of which is justified by the frequent expression of CD30 on the lymphomatous cells, might have an effect, but their efficacy still needs to be demonstrated. AB targeting IL-15 could also be used to treat small cell lymphoproliferation and help to improve the overall therapeutic response by sensitising (or resensitizing) the tumour cells to the CT [38,41]. Their use is under investigation in RCD.

Innovative drugs

Innovative drugs, which are less toxic and which have been reported to be effective in T-cell NHL, even when refractory, have considerable prospects in this area [92]: lenalidomide or Revlimid®, from the immunomodulatory family of drugs (IMiDs) [93]; mammalian target of rapamycin (mTor) inhibitors or Rapamycin® [94]; histone deacetylase (HDAC) inhibitors [95,96]; and new derivatives of dihydrofolate reductase inhibitors (DHFR), such as pralatrexate [97]. JNK inhibitors (found to be activated in RCD) are also being developed. However it is not likely that these drugs will be sufficient for use as single-drug therapy. They could be used either in combination with CT or as maintenance once CR is attained.

The role of high-dose chemotherapy

The role of high-dose CT remains to be better understood for EATL, but its benefit in the treatment of aggressive T-cell NHL appears to be supported by a recently published prospective, multicentric study (grade B study) [84]. It was a cohort of 83 patients, mainly with non-specific PTCL and angioimmunoblastic lymphadenopathy (AILD), and only 5 cases of EATL, i.e., 6% of the cohort. The overall response, following myeloablative conditioning (12-Gray total body irradiation and cyclophosphamide 60 mg/kg × 2 days), was found to be 66%, 56% of which were CR and 8% PR. After a median follow-up of 33 months, over 50% of the patients were alive. Finally, the overall survival and the 3-year RFS with and without CR was 48, 53 and 36%, respectively. Similarly, the Scottish study (grade B) presented at the 2008 ASH (see above) also points to the benefits of auto-PBSCT in the treatment of EATL with results that had never before been obtained until then for this disease [76]. Early (after two or three courses, depending on the bone marrow involvement) and systematic anticipation of peripheral stem cell collection is thus important in patients of all ages who are able to have an autologous transplantation.

Allogeneic bone marrow transplantation

Allogeneic bone marrow transplantation may be the only potentially curative treatment for EATL due to its characteristic resistance to CT. Its role in the management of
aggressive T-cell NHL was recently discussed in a retrospective analysis including 77 patients (grade B study) and seemed to be confirmed since the overall survival and RFS were respectively 57 and 53% at 5 years, with a 33% mortality rate related to the procedure [98]. However, it was mainly a retrospective and heterogeneous cohort made up of non-specific PTCL, anaplastic NHL (AIL), with a single case of EATL, the detailed description of which is not available. In any case, only experimentation with this procedure in patients with EATL will enable its role to be better clarified, provided that the preliminary therapy puts the disease into remission so that patients can receive the transplantation. This therefore justifies HLA typing in patients of all ages that are eligible (up to 60 years), as well as sibling tissue typing and possible consultation of bone marrow registry databases. The type of conditioning must then be planned according to the tumour response already obtained; undoubtedly, attenuated conditioning would be preferable, including monoclonal AB targeting CD52 and fludarabine, especially in cases of underlying RCD but within the limitations previously mentioned [91].

Improving assessment of residual disease

It is important to define homogenous, rigorous and the most sensitive possible endpoints, especially before a transplantation procedure. PET-CT and CT enteroclysis (±MRI enteroclysis), as well as their scheduling in the follow-up monitoring, are currently under investigation for this indication with promising preliminary results. With regard to endoscopic monitoring with biopsies, which is always essential, immunophenotype analysis in cell suspension is of additional value through the isolation of EILs; it is available in specialised centres and is being evaluated for routine use.

Improving the early diagnosis of enteropathy-associated T-cell lymphoma

Improving the early diagnosis of EATL seems to be equally important, as stage is the most important prognostic factor to date [11,12,60,77]. It is necessary to be able to identify and treat the untreated and/or undiagnosed CD. EATL should then be suspected in any adult patient with CD, even if complying with a GFD. Routine serological and endoscopic monitoring should be anticipated after at least 1 year of well-conducted GFD, and as long as histological abnormalities persist, in order to detect CD that is not controlled due to non-compliance with the GFD and/or is refractory or even with low-grade RCS lymphoma lesions already [4,99]. The detection of predictive factors such as HLA-DQ2 homozygotes (as compared to heterozygotes or those carriers of HLA-DQ8), if they are confirmed on larger cohorts, would enable celiac patients who are at significantly greater risk of lymphoma complications (RCD2 and EATL) to be targeted, even if lymphoma must be routinely investigated for in all celiac patients that do not respond to the GFD [36,100]. These latter cases exclude of course the many patients with silent CD in whom there is no possibility for early screening of EATL.

Prevention of EATL

Lastly, the prevention of EATL can be undertaken with two approaches. First, compliance with the GFD, since it significantly reduces the RR of EATL four-fold compared to celiac patients that are continually exposed to gluten [57,58,101]. Secondly, the treatment of RCD2, in which the risk of developing NHL is between 33 and 50% at 5 years [4,16,28,47,75,100], could aid in preventing the emergence of EATL. The long-term results of the combination of high-dose melphalan and fludarabine followed by an auto-PBSCT in cases of RCD2 are not known at this time, but encouraging data have been reported by Al-Toma et al. [68].

Conclusion

EATL is the most highly dreaded complication of adult patients with CD. There are still many unanswered questions to date with regard to its management. There remains much to be done to improve treatment, but the rarity of the disease and the difficulties related to its early diagnosis have delayed potential therapeutic advances. In any case, however, much progress can be expected given its very negative prognosis and much hope is held out for new protocols of CT, of innovative treatments, of immunotherapy and of improvement in the multidisciplinary and overall (symptomatic measurements) management. In any case, only one multicentre and collaborative study [81] which would refer all patients with EATL to a prospective cohort should be able to help us progress in its management and long-term prognosis. These are thus the main objectives of the INCa Lymphoceliac project coordinated by HEGP and Necker hospital centres.

Conflict of interest statement

The authors declare no conflict of interest.

References

Intestinal T-cell lymphoma associated with enteropathy


Intestinal T-cell lymphoma associated with enteropathy


