Enteropathy-Associated T-Cell Lymphoma: Improving Treatment Strategies


Abstract

Enteropathy-associated T-cell lymphoma (EATL) is a rare and usually rapidly fatal intestinal T-cell non-Hodgkin lymphoma. It arises from intraepithelial lymphocytes and has a high association with coeliac disease. The high mortality of EATL is associated not only with the very aggressive and often chemotherapy-refractory nature of the lymphoma. The poor condition of patients due to prolonged and severe malnutrition compromises the ability to deliver chemotherapy. There are no standardized treatment protocols, and the optimal therapy for EATL remains unclear. The primary step of treatment consists of local debulking, preferably as early as possible after EATL diagnosis. Morbidity and mortality seem to rise with advanced stages of disease due to tumour size progression, worse nutritional status and a higher risk of emergency surgery due to perforation. Standard induction therapy for EATL is anthracycline-based chemotherapy, preferably resumed between 2 and 5 weeks after surgery (depending on clinical condition). Intensification of therapy using high-dose chemotherapy followed by consolidation with BEAM and autologous stem cell transplantation is associated with better outcome. Notably, this treatment strategy has only been applied in patients eligible for this aggressive regimen which might reflect selection bias. Unfortunately, prognosis of EATL remains poor; 5-year survival varies from 8 to 60% depending on the eligibility to receive additional steps of therapy. New treatment strategies are urgently needed for a better prognosis of this lethal complication of coeliac disease. Brentuximab vedotin (anti-CD30) might be promising when added to conventional chemotherapy and is suggested as upfront treatment in EATL.

Introduction

Enteropathy-associated T-cell lymphoma (EATL) is a rare intestinal lymphoma that arises from intraepithelial lymphocytes. In Western countries, this lymphoma has a high association with coeliac disease (CD). In patients with CD, EATL is identified as the main cause of increased mortality [1, 2] and develops in an estimated 0.04% of adult-onset CD patients [3]. Based on clinical presentation, EATL can be divided into two subtypes: pri-
mary and secondary EATL. Primary EATL develops without a preceding history of CD. The first presentation could be perforation or obstruction, which leads to the diagnosis of both EATL and CD. Secondary EATL is diagnosed in patients with well-established CD or refractory CD type II (RCDII). These patients deteriorate and eventually develop EATL.

There are no validated and standardized treatment protocols for EATL due to the rarity of this disease. Treatment strategies consist of different additional steps, including surgery, chemotherapy and stem cell transplantation (SCT), each applied depending on the eligibility of the patient. EATL patients are characterized by acute malnutrition, due to both malabsorption and an alleged hypermetabolism [4]. Besides the aggressive and often chemotherapy-refractory nature of the T-cell lymphoma itself, the deprived nutritional status of most EATL patients at diagnosis seems to be an important factor which negatively affects clinical condition and therefore preventing the use of aggressive treatment strategies. This results in an extremely variable 5-year survival of EATL patients between 8 and 60% [5–11].

Since no standard therapeutic regimens are established in EATL and clinical condition is highly variable, a range of therapeutic strategies have been used. So far, treatment of EATL is only centralized in a minority of cases. This year, the European Reference Network of Coeliac Disease was started up to build a uniformly network in the field of (pre-)malignant CD. The aim of this network is to facilitate uniform standardized diagnostic and therapeutic care and to perform translational research in this field. In this paper, we summarize recently published data on different treatment strategies and present future perspectives according to the European Reference Network.

**Standard Induction Therapy**

Historically, patients with EATL were treated with surgery, chemotherapy or a combination of both. Unfortunately, there is a shortage of prospective observational studies, although patients with EATL have in some cases been included in trials for aggressive lymphoma. In general, chemotherapy is probably the most important factor of improved survival in lymphoma patients [12]. Due to the risk of bowel perforation during chemotherapy or symptomatic perforation or stenosis at diagnosis, the preferred first step in the treatment of EATL is surgical debulking, whether or not followed by subsequent chemotherapy. The frequency of early and late post-operative morbidity is relatively high after surgical debulking [13]. Early complications mainly include anastomotic leakage and sepsis. Stenosis at the side of the anastomosis is the most frequently reported late complication. Mortality is higher when the resection is performed in the acute setting. Resection of the tumour mass, preferably as early as possible after diagnosis, improves survival and improves the ability to receive chemotherapy after resection [8, 13].

Standard induction chemotherapy regimens applied in EATL are usually anthracycline based consisting of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) in most cases [8, 10, 12]. Five-year survival percentages following surgical debulking and standard induction chemotherapy vary from 8 to 28% [7–9, 14]. The most common reason for withholding chemotherapy after surgical debulking is a poor condition of the patient after surgery. Furthermore, a considerable proportion of EATL patients are unable to complete chemotherapy due to poor nutritional status, rapid progression of disease during treatment, and local or systemic complications [11].

As shown in different independent studies, patients with secondary EATL have a less favourable outcome than EATL patients without a prior diagnosis of CD [8, 9, 15]. Within the group of secondary EATL, patients who suffer from refractoriness to the gluten-free diet (RCDII) even have a worse prognosis. A potential explanation relates to the fact that these patients generally suffer from severe and long-standing malnutrition [4, 8].

Overall, patients treated with combination therapy consisting of surgical debulking and subsequent standard induction chemotherapy show a significantly better outcome than those treated with standard induction chemotherapy or surgery alone [7–9, 14]. This stresses the importance of early diagnosis of EATL and extensive nutritional assessment to optimize nutritional status at diagnosis and during therapy.

**Treatment Intensification**

As the role of standard induction chemotherapy (CHOP) combined with surgical debulking obtained persisting dismal survival percentages, several novel strategies are being assessed in EATL treatment. In the last decades, treatment intensification using high-dose chemotherapy and consolidation with hematopoietic SCT as upfront therapeutic option has become an increasingly accepted treatment option for aggressive T-cell non-
Hodgkin lymphomas (NHL). Two recent studies showed significant improvement of prognosis in patients treated with intensified chemotherapy (CHOP combined with etoposide [5, 6] or methotrexate [5, 7]) followed by auSCT. The specific effect of new drug combinations and intensified chemotherapy is somewhat difficult to evaluate due to a combination with SCT in most studies and the selected patient category. These studies showed a lower amount of patients failing the high-dose chemotherapy due to disease progression as compared to anthracycline-based chemotherapy. Moreover, patients treated with high-dose chemotherapy and autologous SCT (auSCT) had higher remission rates than those treated with standard induction therapy including CHOP and additional auSCT [9–11]. However, as expected, there was a higher incidence of neutropenic fever and sepsis compared with standard induction chemotherapy. This supports the notion that intensification of induction therapy might increase eligibility in EATL patients to ultimately achieve SCT.

Consolidation Therapy

As mentioned, consolidation with BEAM (carmustine, etoposide, cytarabine, melphalan) and autologous haematopoietic SCT (auSCT) has become increasingly accepted for EATL treatment. The rationale for using this strategy is tumour and immunoablation using high-dose chemotherapy, with subsequent regeneration of naïve T-lymphocytes derived from reinfused haematopoietic progenitor cells. During induction chemotherapy, stem cells are harvested by leukapheresis and are re-infused after high-dose, myeloablative BEAM chemotherapy. Various independent studies have demonstrated that auSCT combined with intensified chemotherapy and resection is feasible, also in patients with CD, and shows the most favourable outcome. Outcome for those treated with intensified chemotherapy followed by auSCT improved to a 5-year overall survival of 50–60% [6, 7]. It should be noted that these studies included a variable EATL population consisting of only primary EATL [7], various types of peripheral T-cell NHL [6] or EATL patients in whom various chemotherapy schemes preceded the auSCT [5]. In series evaluating the complete EATL population, consolidation therapy using SCT also appeared to increase survival [8, 9], although this was non-significant due to the limited amount of patients in these studies eligible for auSCT and a limited time of follow-up.

These results clearly support the idea that patients tolerating more intensive approaches may benefit. Since SCT has only been applied in patients eligible for this aggressive regimen, it remains to be seen whether adding SCT can make a significant impact on survival in all EATL patients, and international trials to evaluate this are therefore urgently needed.

Experimental Treatment Strategy

Based on the theory that allogeneic SCT (alloSCT) might be more effective than auSCT in EATL treatment due to a graft-versus-lymphoma effect, the effect of alloSCT in EATL has been assessed. However, results are conflicting. In some centres, patients who underwent alloSCT died within 2 months after transplantation due to EATL relapse [9]. Others showed alloSCT to be successful in 2 out of 3 patients treated with this regimen [8]. We hypothesize that a dismal outcome in alloSCT in some cases might be due to insufficient conditioning or a delay in the graft-versus-lymphoma effect due to the immunosuppressive medication used. Whether alloSCT has a role in treatment of EATL remains to be evaluated in future experimental prospective trials.

Future Perspectives

Due to the fact that only a limited percentage of EATL patients ultimately achieve the most aggressive consolidation step, recent studies assessed intensification strategies consisting of new chemotherapy combinations and a higher dose as described above [6, 7]. Besides high-dose chemotherapy, the evidence for the effectiveness of target therapy with monoclonal antibodies (mAbs) is increasing. Owing to their excellent potential for specific detection, delineation and selective treatment of systemic diseases, mAbs are broadly used as a treatment strategy in malignancies as B- and T-cell NHL. The rationale for using this strategy is based on the utilization of the antigens expressed by tumour cells and to deliver cytotoxic agents inside the malignant cell based on this antigen expression using antibody-drug conjugates.

EATL type I is a large-cell lymphoma and is highly associated with CD30 [16]. This type of T-cell NHL is characterized by the expression of CD30 in the majority of cases [17]. CD30 is an ideal target for mAb therapy due to its limited expression on normal tissues. Brentuximab vedotin is an anti-CD30 antibody which is conjugated to
the anti-microtubule agent monomethyl auristatin E [18]. Following binding to CD30, brentuximab vedotin leads to cell cycle arrest and apoptosis of the tumour cell. Several studies showed this agent to be well tolerated and highly active in patients with relapsed Hodgkin’s lymphoma [19], systemic anaplastic lymphoma or primary cutaneous T-cell NHL [18]. The most frequently reported adverse event is peripheral neuropathy [20].

This impressive response might be very promising for the relatively chemotherapy-refractory nature of EATL, and has been described to be effective for EATL in a case description [21]. Preliminary data in a limited number of EATL patients described by Malamut et al. [8] show multi-agent therapy consisting of intensive chemotherapy combined with anti-CD30 followed by consolidation with BEAM and auSCT to be safe and effective, although longer follow-up will be required. The European Reference Network of Coeliac Disease suggests implementing a uniform treatment strategy in Europe including brentuximab vedotin. This network was started up this year and consists of haematologists, gastroenterologists, researchers from the major (R)CD-referral centres in Europe (including Paris, Amsterdam; more centres are expected). The suggested treatment protocol is outlined in figure 1 and combines high-dose chemotherapeutic drugs, which are proven to be effective (CHP/MTX), with anti-CD30 targeted therapy (brentuximab vedotin) with the aim to improve the number of patients able to proceed to BEAM and auSCT.

Ultimately, the best way to treat EATL would be to prevent it. Therefore, stringent strategies for early EATL diagnosis in patients with uncomplicated CD or RCDII should be implemented. One of the options suggested by the European Reference network would be to perform radioactive labelling of mAbs with brentuximab vedotin. Since patients with RCDII show no CD30 expression on the intra-epithelial lymphocytes and EATL is characterized by CD30 expression, organ and whole-body distribution of the labelled product can be assessed using PET imaging, and early EATL development could be made more or less likely using this strategy. Besides imaging strategies for early diagnosis, brentuximab vedotin might be used for in vivo research to understand the biological process and the pathogenesis of EATL development in CD and RCDII patients. Furthermore, early diagnosis and effective treatment of RCDII is of utmost importance for secondary prevention of EATL.

**Fig. 1.** Phase 2 study of brentuximab vedotin and CHP followed by auSCT as frontline treatment of EATL. SD = Stable disease; PD = progressive disease. Study coordinators: Prof. Hermine, Prof. Cellier, Dr. Sibon (Paris).
Conclusion

In conclusion, prognosis for EATL patients remains extremely poor. Most studies indicate that optimising nutritional status and combination therapy including both surgical debulking and standard induction chemotherapy should be the standard of care for these patients. In addition, some studies suggest that intensification with upfront high-dose chemotherapy and consolidation using auSCT may further improve disease control and survival, although this aggressive treatment strategy is only available for a limited amount of patients. Considering the need for a uniform treatment strategy in order to combine highly specialized care and translational research in this field, we would highly suggest adding brentuximab vedotin and methotrexate to the standard induction chemotherapy in EATL patients and to perform easy accessible consolidation with BEAM and auSCT in patients aged <70 years.

Disclosure Statement

All authors state there is no actual or potential conflict of interest to disclose in relation to this article.

References

4 Wierdsma NJP, Nijeboer MAE, de van der Schueren M, Berkenpas AA, van Bodegraven AA, Mulder CJ: Refractory coeliac disease and EATL patients are characterised by malnutrition and malabsorption at presentation; a comparative study with a newly diagnosed Coeliac Disease patients (abstract). Digestive Disease Week, Chicago, May 2014.