Today's treatment of diffuse large B cell lymphomas in adults

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Classification of DLBCL and prognostic stratification

Diffuse Large B cell Lymphomas (DLBCL) are the most common type of non-Hodgkin's lymphoma), with the incidence rising from 2 cases per 100,000 at 20-24 years of age to 112 cases per 100,000 by 80-84 years (Yancik and Ries 2004). In the 2008 WHO Classification of Haematological Malignancies, the category of DLBCL includes a number of disease variants/entities all characterized by being rapidly growing mature B cell tumors with large or relatively large cells (Table 1). With the exception of the Primary CNS DLBCL, all types of DLBCL are broadly treated in a similar way.

Immunophenotyping is an essential diagnostic procedure which allows DLBC lymphomas to be identified and allows DLBC lymphomas to be further divided into germinal centre (GC) type (CD10 + or CD10-, BCL6+ MUM1-) and non GC type (CD10-BCL6- or CD10 – BCL6+ MUM1+) (Hans *et al*. 2004). It had been shown that this GC/non -GC stratification provides valuable prognostic information, but the supporting data mainly related to the pre-rituximab era. The prognostic value of the so-called Hans algorithm is less clear in patients treated with immuno-chemotherapy as opposed to CHOP alone (Nyman *et al*. 2007). Prognostic discrimination can also be achieved with gene expression profiling (GEP) (Alizadeh *et al*. 2000, Rosenwald *et al*. 2002,Rosenwald *et al*. 2003) sub-dividing DLBC lymphoma into GC types, activated B cell (ABC) types and also Primary Mediastinal B cell Lymphoma (PMBL). The prognostic stratification between GC and ABC subtypes remains valid in patients receiving immunochemotherapy (Lenz *et al*. 2008). Further prognostic information can also be obtained by analysis of the reactive stromal signatures (Lenz *et al*. 2008). GEP is technically demanding, however, and robust kits have not entered routine use either for broad based diagnosis or DLBC sub categorisation. Recently a new immuno-histochemistry algorithm has been developed which places less weight on BCL6 staining to identify GC-like lymphomas, than in the Hans algorithm, and additionally uses Germinal Centre B cell Expression Transcript 1 (GCET1) for this purpose, and high level FOXP1 staining to assist in the identification of ABC lymphomas (Choi *et al*. 2009). Importantly, this algorithm has over 90% concordance with the classification derived from GEP.

The GC-like lymphomas probably arise from normal germinal centre B cells and are associated with the t(14;18) translocation, deletion of PTEN, amplification of the microRNA cluster miR-17-92, and p53 mutations (Lenz and Staudt 2010). The ABC Lymphomas are thought to originate from a post-germinal centre B cell and are characterized by activation of the NFkB and JAK kinase signalling pathways and a number of recurrent mutations in the B cell receptor (CD79 genes), CARD11, BCL10 and MALT1(CPM complex). A20, the negative regulator of NFkB signalling, has been identified, which gives rise to these signalling events. BCL2 is usually over-expressed and p16 is often deleted (Lenz and Staudt 2010). Recently it has also been shown that over 30% of ABC lymphomas have a mutation in the MYD88 gene which codes for an adaptor protein that mediates toll and IL-1 receptor signalling (Ngo *et al*. 2010). This also results in activation of NFkB and JAK kinase. The presence of NFkB activation in a subgroup of patients raises the possible value of using NFkB inhibitors in standard therapy and randomized trials are in progress. At the current time there is no evidence that this is beneficial and GEP and mutational screening thus remain experimental investigations.

Prognostic information can also be summarized from a number of clinical features including age, performance status, stage of the disease, number of extranodal disease sites and the LDH level. These parameters are used to form the International Prognostic Index (IPI) (1993) (Table 2), which identifies four risk groups: low, low intermediate, high intermediate and high. An age adjusted (AA) IPI is widely used for stratification and analysis of clinical trials. The data for the IPI again derives from the pre-rituximab era, and when immuno-chemotherapy is used as first line treatment, the IPI appears less discriminatory in some series (Sehn *et al*. 2007) but not in others (Ziepert *et al*. 2010). Sehn and colleagues (2007) suggested a modification to the distribution of the number of risk factors in the different risk categories, and reduced the number of risk groups to three: very good, good and poor. This index, they suggest, remains informative in the post rit-

Table 1. Diffuse Large B cell Lymphoma: variants, subgroups and subtypes, entities.

Diffuse Large B cell Lymphoma not otherwise specified
Diffuse Large B cell Lymphoma subtypes
T cell/ histiocyte rich large B cell lymphoma
Primary DLBCL of the CNS
Primary cutaneous DLBCL, leg type
EBV positive DLBCL of the elderly
Other lymphomas of large B cells
Primary mediastinal large B cell lymphoma
Intravascular large B cell lymphoma
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
ALK positive LBCL
Plasmablastic lymphoma
Large B cell lymphoma arising in HHV8-associated multicentric Castleman's disease
Primary effusion lymphoma
Borderline cases
B cell lymphoma, unclassifiable, with features intermediate between DLBC lymphoma and Burkitt lymphoma
B cell lymphoma, unclassifiable with features intermediate between DLBC lymphoma and classical Hodgkin's lymphoma

From WHO Classification of Tumors of Haematopoietic and Lymphoid tumors. Ed Swerdlow SH et al. Lyon 2008.

Table 2. Charlson Weighted Comorbidity Index (adapted from Charlson *et al.* 1987: J. Chronic Dis 40: 373-83).

Assigned weights for diseases	Condition
1.	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebro vascular disease Dementia Chronic pulmonary disease Corrective tissue disease Mild liver disease Diabetes without end organ damage
2.	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any malignancy
3.	Moderate or severe liver disease
6.	Metastatic solid tumour

Total score obtained by adding up assigned weight for each co-morbidity present.

uximab era. In elderly patients, however, there are no very good risk patients, leaving only two risk categories. For this reason, Advani *et al*. (2010) have added a risk factor of age over 70 yrs in the elderly (over 60's) IPI.

The anatomical staging used in the IPI and its modifications is based on the Ann Arbor staging system, and this mandates the careful taking of the history and performance of a physical examination. It is frequently stated that this should include the examination of Waldeyer's ring, but this requires considerable expertise and is less necessary with modern imaging of the head and neck. The standard imaging procedure is a CT scan of neck, chest, abdomen and pelvis, and MRI scanning is mainly used to better define bony abnormalities or neurological lesions. Whole body PET scanning is now widely used during diagnosis, but this should not be considered as mandatory except perhaps in an apparently localized disease where a curtailed course of chemotherapy and radiotherapy is being considered. It can be argued that a PET scan is highly useful in assessing response to treatment at various stages of the disease and that a baseline investigation at diagnosis is valuable. However, DLBC lymphomas are nearly always PET positive, and the expense of the baseline scan is not readily justifiable. Furthermore, improved response identification is only mandatory if the knowledge obtained can be used to modify treatment and improve outcome. Such data is currently lacking. PET scanning at diagnosis may identify bone marrow deposits and obviate the need for a bone marrow biopsy, a potentially unpleasant procedure, but both false positives and false negatives occur (Carr *et al*. 1998).

Treatment

The modern treatment of DLBC lymphoma has been defined by four major advances in the last seventy years. First, in the 1940s, was the introduction of high voltage radiotherapy which resulted in cures in a small proportion of the patients with localized disease, and radiotherapy still has a role in localized disease. Given alone to Stage IA patients with non-bulky diffuse large cell lymphomas, the cure rate was about 50% with the majority of failures due to progression outside of the radiation field (Vaughan Hudson B *et al*. 1994). With modern imaging including PET scanning, those patients still defined as Stage 1A should therefore have much better results with RT alone, although studies have not been carried out to demonstrate this. Radiotherapy alone may have a role in the frail elderly patient with a localized disease if chemotherapy cannot be tolerated. Standard practice for Stage IA disease is to administer combined modality therapy with reduced duration chemotherapy (typically 3 or 4 courses of CHOP) followed by consolidation RT (Miller *et al*. 2000). The standard dose of RT was traditionally 35-45 Gy but lower doses of RT are probably sufficient (Hoskin *et al*. 2005). In some centers this type of strategy would also be applied to Stage IIA patients without risk factors, but the results appear to be less satisfactory. One study has suggested that radiotherapy is unnecessary, at least in older patients, even after only three cycles of CHOP (Bonnet *et al*. 2007), and a previous French trial suggested that a full course of ACVBP chemotherapy was superior to CHOPx3 followed by radiotherapy in younger patients (Reyes *et al*. 1993), Recent Phase II trials have reported encouraging results when rituximab was added to CHOP plus radiotherapy in localized disease (Persky *et al*. 2008) but whether this is better than CHOP plus rituximab alone without radiotherapy is not known. Radiotherapy may also have a place in the consolidation of initial bulk disease, and partial remissions

if the persisting disease is localized, but the limited data advocating such approaches predates the CT/PET scan era and there is now greater uncertainty. This is well illustrated by Primary Mediatsinal B cell Lymphoma, where the disease is often bulky at presentation and a post-treatment residuum is usual (Boleti and Johnson 2007). Whether or not to give consolidation in a PET negative patient with a residual mass remains controversial.

The next major advance was the development of the CHOP combination chemotherapy regimen (MeKelvey *et al*. 1976), which resulted in long term survivals in about 30% of stage III and IV histologically aggressive lymphomas. Further improvements in outcome occurred over the next two decades, which can be best ascribed to improvements in supportive care. This certainly included better antibiotics and the improved management of neutropenic sepsis, but probably equally important was the greater physician confidence allowing the delivery of more cycles of chemotherapy at full dose without delay. The development of G-CSF has probably contributed to the increase in physician confidence (see below), but in a trial carried out in the UK in the 1990s, the 5 year OS for Stage III/IV patients with an additional poor prognostic factor was nearly 50% following treatment with CHOP alone – about 15% better than 2 decades earlier. This was achieved without G-CSF prophylaxis (Linch *et al*. 2010).

The fourth advance was the addition of the CD20 monoclonal antibody rituximab to chemotherapy. In the seminal GELA LNH 98-5 randomized trial where rituximab 375 mg/m^2/IV was added (or not) to classical CHOP for eight cycles in elderly patients with DLBC, there was a significant improved in outcome associated with the use of rituximab (Coiffier *et al*. 2002). The 5 year PFS was 54% in the R-CHOP patients compared to 30% in CHOP patients (p = 0.00001). The corresponding 5 year OS rates were 58% and 45% respectively (p = 0.0073) (Feugier *et al*. 2005). The benefit was seen with both low and high risk disease as defined by the AA IPI. Broadly confirmatory results were seen in a US Intergroup trial (Habermann *et al*. 2006) and benefits were also demonstrated in younger patients with good prognosis in the MInt trial (Pfreundschuh *et al*. 2008). The value of rituximab was also shown when it was combined with time-intensifed R-CHOP14 (Sonneveld *et al*. 2006, Pfreundshuh *et al*. 2008,). There is no robust randomized trial data for the value of rituximab in younger patients with poor prognostic disease, and such trials are no longer feasible. Population based studies do not, however, suggest that the impact of rituximab will be lost in this group of patients (Sehn *et al*. 2005).

The optimal rituximab regimen has not been determined. The dose of 375 mg/m^2 is somewhat arbitrary and the three weekly frequencies of rituximab infusions in CHOP-R_{21} were designed on logistic rather than pharmacokinetic principles. Indeed Reiser *et al*. (2006) has shown that, even with a CHOP14 schedule, peak CD20 serum levels are not attained until after 5 cycles of therapy, and they are therefore testing a dose-dense rituximab regimen (Poeschel *et al*. 2006) which gives peak CD20 levels from the start of therapy. There is no evidence that maintenance rituximab is of value in DLBCL. In the US, Intergroup trial patients with DLBCL were treated with CHOP and a 2 x 2 randomization for rituximab induction, or not, with the CHOP chemotherapy and for rituximab maintenance therapy or not. Rituximab maintenance resulted in a significant improvement in those patients treated with CHOP alone, but not in those who received R-CHOP as induction therapy (Habermann *et al*. 2006).

Prior to the development of rituximab, research was focused on the addition of more drugs to the CHOP regimen and the shortening of the intervals between each cycle of therapy. The initial encouraging results with multi-agent regimens proved to be a false dawn (Fisher *et al*. 1993), although several of the so-called third generation regimens probably did not deliver higher dose intensity, and in order to give more drugs, the dose of the most efficacious agents was reduced in some regimens. The anthracycline dose is lower in some of the equally effective weekly regimens such as PMitCEBO (Burton *et al*. 2006), than in a full course of CHOP, and might still warrant consideration in some frail patients, where close monitoring is required. The German high grade lymphoma group added etoposide to CHOP and found this to be beneficial in younger patients with good prognosis disease (Pfreundschuh *et al*. 2004a). In older patients of both good and poor prognostic risk, they found that shortening the interval between cycles of CHOP from 21 to 14 days with mandatory G-CSF resulted in improved outcome (Pfreundschuh*, et al*. 2004b). The HOVON group also compared standard CHOP-21 with an intensified 2-weekly CHOP regimen (CHOP-I) in patients with aggressive lymphoma up to the age of 65 years, and in this trial, the minor advantage seen for CHOP-I was not significant (Verdonck *et al*. 2007). Several studies have subsequently compared CHOP14 plus rituximab with CHOP21 plus rituximab, and the early reports suggest that the advantage of the time intensification is no longer maintained (Cunningham *et al*. 2010). In France, a randomized trial also showed an advantage for a more intensive 5 drug regimen (ACVBP), compared to CHOP, in patients with poor-risk aggressive lymphoma between the ages of 61 and 69 years (Tilly *et al*. 2003). The CR rate was similar (58%vs 56%), and despite more treatment related deaths in the ACVBP arm, there was improved EFS (39% vs 29% p=0.005) and OS (46% vs 38% p=0.036). GELA are currently comparing CHOP-R with ACVBP-R in a younger patient population.

Central nervous system CNS prophylaxis

The incidence of CNS progression or relapse in DLBCL is about 5% in most series (Macmillan 2005) and although the seminal trial of R-CHOP did not show a reduction in CNS relapse (Feugier *et al*. 2004), a reduction was apparent in the RICOVER-60 trial (Boehme *et al*. 2009). An analysis of the British Columbia population-based registry suggested a similar reduction in CNS progression or relapse (Villa *et al*. 2010). It is a commonly held belief that if the risk of CNS relapse is sufficiently low, CNS prophylaxis is not justified in all patients, and much attention has been placed on the identification of risk factors for secondary CNS disease (Macmillan A 2005). The risk factors for CNS progres-

sion/relapse are similar to those in the IPI (eg advanced stage, more than one extranodal site and a raised LDH level) and some groups use the IPI to determine who should receive CNS prophylaxis, restricting prophylaxis to high/intermediate and high risk disease. A number of other anatomical sites have been identified as risk factors which include testis, paranasal sinuses, the epidural space and possibly the breast. Hegde and colleagues (2005) have suggested that flow cytometry of the cerebro-spinal fluid (CSF) may enable improved risk stratification. They used sensitive multicolour flow cytometry to detect light chain restricted B cell clones in 51 newly diagnosed patients at risk of CNS disease. One had lymphoma cells detected by standard cytomorphology and a further 10 had small lymphoma clones only detected by flow cytometry. A Spanish co-operative group have recently reported their experience of flow cytometric assessment of the CSF in 67 patients with DLBCL at high risk of CNS disease (Sancho *et al*. 2010). Of the 67 patients, 56 (84%) had negative CSFs by both morphology and flow cytometry, one patient had CNS lymphoma detected by both cytomorphology and flow cytometry, and 10 patients had occult lymphoma in the CSF only detected by flow cytometry.. The most frequently used prophylaxis is intra-thecal methotrexate or cytosine arabinoside, but this is not ideal. Apart from the fact that up to a half of CNS progressions/relapses occur in the context of widespread disseminated disease, CNS relapse is frequently parenchymal and not lepto-meningeal. If intrathecal cytotoxics are to be given, however, the possible use of liposomal ara-C, which has a prolonged half life in the CSF (Glantz *et al*. 1999) and will allow reduced numbers of lumbar punctures, is an attractive option but has not been rigorously tested in randomized trials. In the ABCVP vs CHOP trial mentioned above (Tilly *et al*. 2003) there were significantly fewer isolated CNS relapses in the ACVBP arm with an incidence of only 2.2% with ACVBP compared to 5.8% with CHOP. It should be emphasised that in the ABCVP arm there are not only 4 intrathecal injections of methotrexate but there are also 2 intravenous high dose methotrexate infusions. It is likely that the intravenous methotrexate is key to the low CNS relapse rate. Clearly randomized trials of CNS prophylaxis are necessary but very large trials are required to demonstrate a significant effect on CNS relapse rate.

Transplantation as a component of initial therapy

A number of studies have explored the value of high dose therapy and autologous stem cell transplantation for patients achieving either PR or a CR after initial therapy. The results have been conflicting and a series of meta-analyses concluded that there was no benefit (Simnet *et al*. 2000, Strehl *et al*. 2003, Greb *et al*. 2008). There were three trials, however, that reported a benefit following an autograft (Haioun *et al*. 2000, Milpied *et al*. 2004, Gianni *et al*. 1997), and although this may represent the random chance, it is still possible that differences in the protocols accounted for the favorable results. In both the Haioun and the Milpied study it is noteworthy that an intensified CHOP regimen had been used initially and nearly all the patients were in CR at the time of transplantation. Even if there was a real benefit from consolidation high dose therapy in this situation, it does not mean that this still pertains in the rituximab era, and further trials would be needed. If high dose therapy is of greatest benefit in patients already in CR, then the use of rituximab in induction might increase the proportion of patients in whom high dose therapy would be beneficial, but with the improved results from rituximab, it can be argued that there is less need for an intensive consolidation procedure and it will be more difficult to demonstrate any superiority associated with the high dose therapy. There is currently, therefore, little enthusiasm for autologous transplantation in DLBCL as a component of initial therapy. Similarly there is no role for allogeneic transplantation in first remission.

Treatment of relapse

In those patients either failing to achieve CR or relapsing from CR, who are young and fit enough to receive high dose therapy, the aim must be to induce a remission with second line standard dose regimens and then to proceed to a high dose therapy procedure. In the PARMA trial (Philip T *et al*. 1995), the event-free survival at 5 years after an autograft was 46% compared to 12% in the non-transplanted patients, and the respective overall survivals were 53% and 32%. A large number of second-line regimens have been developed but here has only been one large randomized trial comparing such regimens in DLBCL (Gisselbrecht *et al*. 2010). This showed that the efficacy of R-ICE and R-DHAP were broadly similar. It is standard practice to add rituximab to the second line regimen but whether this is appropriate if the patient has failed while, or soon after, receiving rituximab is debatable. A number of studies showed that it was only advisable to proceed to an autograft if the patient had responded to initial salvage therapy with response being defined by clinical and CT critieria (Philip *et al*. 1987, Gribben *et al*. 1989). With CT/PET scanning now widely available, it appears that autografts are of major benefit only in those patients with no metabolically active disease (Spaepen *et al*. 2003), and further attempts with standard dose therapy should be made to achieve such a state before proceeding to an autograft. The patients failing to achieve a metabolic CR after initial salvage therapy clearly represent a poor prognostic group, and there is enthusiasm for considering these patients for reduced intensity allografts. One study has suggested that the allograft procedure overcomes the poor prognosis associated with a persistently positive PET scan (Lambert *et al*. 2010), but this requires confirmation. It is clear that patients who have received rituximab as part of initial therapy fare less well when they fail that therapy than the group of patients who failed non-rituximab containing regimens (Gisselbrecht *et al*. 2010). This is largely because they have lesser responses to the second line standard dose chemotherapy, and there is no evidence that the outcome of autografting is worse in those who still respond adequately to the second line therapy. Currently the major role of reduced intensity allogeneic transplantation (RIT) is in

those patients who have failed an autograft or in whom an autograft is not possible, and the results from some centers are encouraging. Thomson *et al*. (2009) reported on the use of RIT in 48 consecutive patients with DLBCL (18 transformed from follicular lymphoma), 69% of whom had failed a previous autograft. The overall survival at 4 years was 47%. Less favorable results have been reported from some other centers, and stringency of patient selection is likely to be a major reason for such discrepancies.

The anthracycline problem

It is well established that the total cumulative dose of doxorubicin is the major risk factor for doxorubicin related congestive heart failure (CHF) (Von Hoff, *et al*. 1979), and an upper cumulative limit of 450 mg/m^2 is usually employed. Even at this total dose, cardiac function is compromised in some patients. The risk of CHF increases with age, a history of coronary artery disease, valvular heart disease, diabetes, cigarette smoking, obesity and particularly hypertension (He, *et al*. 2001, Hershman, *et al*. 2008). It is essential that hypertension is well controlled before and during anthracycline therapy. Attempts have been made for over 30 years to develop novel anthracyclines, or derivatives thereof, which have an improved therapeutic window. Epirubicin can be used at cumulative doses nearly double that of doxorubicin without increased cardiotoxicity (Minotti *et al*. 2004), but it has mostly been used at doses considerably lower than two-fold that of doxorubicin. This undoubtedly results in less cardiotoxicity (Smith *et al*. 2010), but uncertainty still remains about its efficacy at those doses. Zinzani and colleagues (1995) substituted doxorubicin 50 mg/m^2 with Idarubicin 10 mg/m^2 in the CHOP regimen and found equal efficacy of CHOP and CIOP with less cardiotoxicity in the Idarubicin containing arm. However when this regimen was tested in a UK trial, CIOP was found to be significantly less efficacious than standard CHOP (Burton *et al*. 2005), and a subsequent study by Trumper *et al*. (2002) suggested that the equivalent dose of Idarubicin, to 50 mg/m^2 of doxorubicin was 14 mg/m^2, at least in terms of myelosuppression. Pixantrone is an aza-anthracenidione structurally similar to mitoxantrone and is the latest anthracycline-like agent to be developed with the aim of minimizing cardiotoxicity without reducing efficacy. Some of the early phase results are encouraging but much larger and more robust trials are still needed (Mukherji and Pettengell 2010).

An alternative strategy is to use doxorubicin incorporated into liposomes. A Cochrane meta-analysis suggested that the liposomal form had similar oncological activity to doxorubicin with a lower rate of clinical and sub-clinical heart failure (van Dalen *et al*. 2008). There have been no phase III trials in lymphoma and liposomal doxorubicin is not licensed for this purpose. There have, however, been some encouraging early phase trials replacing standard adriamycin with a liposomal form in the CHOP regimen (Tsavaris *et al*. 2002, Visani and Isidori 2009) and further studies are clearly justified.

Dexrazoxane is an iron chelator which inhibits hydroxyl radical formation and decreases anthracycline-induced oxidative stress, which is thought to be the major cause of cardiac damage. The Cochrane meta-analysis (van Dalen *et al*. 2008) and a more recent systematic review (Smith *et al*. 2010) indicate that dexaroxane significantly reduces the risk of congestive heart failure associated with anthracycline use. There is still concern however, that the generation of ROS could play a part in anti-tumor activity (Swain and Vici 2004) and there has been reluctance to recommend its use in patients with potentially curable lymphomas. Currently, doxorubicin without a cardio-protectant remains the anthracycline of choice.

Use of G-CSF

G-CSF prophylaxis following chemotherapy reduces the incidence and duration of severe neutropenia and is associated with a reduction in infective episodes. The strongest predictor for haematoxicity is febrile neutropenia in a previous cycle of therapy, but as the greatest risk of infection is with the first cycle of therapy (Lyman and Delgado 2003), G-CSF should be given from the first cycle of chemotherapy. A systematic review and meta-analysis of randomized trials of G-CSF prophylaxis in patients with a variety of different cancers showed a significantly lower early mortality associated with G-CSF use (Kuderer *et al*. 2007) but not a significantly different overall survival. The rationale for G-CSF use has been largely based on pharmaco-economic considerations. Initial cost-minimization assays suggested that G-CSF should be used with any regimen where the risk of febrile neutropenia exceeded 40% (Lyman *et al*. 1993), but when certain indirect costs were taken into account, this threshold was brought down to 20% (Lyman *et al*. 1998). In an analysis of 1246 lymphoma patients treated with CHOP, R-CHOP or CNOP, without early G-CSF, 217 (17%) developed febrile neutropenia, below the 20% threshold (Lyman and Delgado 2003). In a prospective observational study of CHOP recipients (Pettengell*, et al*. 2008), the incidence of febrile neutropenia was 22%. It this seems that CHOP is a marginal regimen form the viewpoint of G-CSF prophylaxis and it should only be used when there is an additional factor for development of febrile neutropenia such as advanced age. Consideration should also be given to the fact that in Europe the cost of G-CSF has plummeted in recent years and a threshold level below the 20% rule may now be appropriate. Pegylated G-CSF, with a prolonged half-life, is an attractive and effective option, but the pharmaco-economic arguments are no longer so compelling.

Treatment of the elderly patient with DLBCL

A recent analysis of cancer registries revealed that the long-term survival of patients with NHL is improving, but for elderly patients the survival in Europe has lagged behind that in the USA (van de Schans *et al*. 2010). There are many possible reasons for this, but one possibility is that it reflects subtle differences in physician attitudes toward the elderly and differences in the expectations of the elderly patients. Every effort must be made to deliver

intensive therapy with curative intent to those elderly patients who can tolerate such therapy, but such a strategy demands greater attention to the evaluation of each individual patient. This must not only happen before chemotherapy starts, but also before each cycle of therapy, with attention to control of hypertension and other concomitant disease, and detection of the signs and symptoms of incipient heart failure or neuropathy. Interim echocardiography should also be performed.

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