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Primary central nervous system lymphoma – Biological aspects and controversies in management ☆

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ABSTRACT

Introduction: This review was produced from the workshop on primary central nervous system lymphoma (PCNSL) at the European Cancer Conference (ECCO 13) in Paris in 2005. It covers the presentation and biological features of the disease (Professor Khe Hoang-Xuan). The role of chemotherapy, including the management of intraocular lymphoma and the use of high dose chemotherapy followed by autologous stem cell transplantation for PCNSL, is discussed (Dr. Andres Ferreri) as well as controversies in the use of whole brain radiotherapy (WBRT) after chemotherapy (Dr. Michele Reni).

The topics covered with discussants at the workshop are also summarised.

Conclusion: The imaging of the brain and the histopathology including detailed immunohistochemistry is of vital importance in making an accurate diagnosis of the disease and understanding the extent of spread of the disease in the CNS. The importance of high dose methotrexate (HDMTX; dose $\geqslant 1$ g/m^2), as the most active drug in the treatment of PCNSL, is stressed. The authors recommend that HDMTX alone or in combination with other active chemotherapy agents should be used to treat PCNSL followed by whole brain radiotherapy (WBRT) unless contraindicated because of the advanced age of the patient and existing cognitive impairment. Only published protocols should be used unless the patient is to be offered a trial that has either national or international support. Baseline neuropsychological tests should be carried out before treatment and repeated during and after treatment. The risks of cognitive impairment associated with the disease, with methotrexate – containing chemotherapy and with whole brain radiotherapy should be explained to patients and relatives when obtaining informed consent. Long-term survival, with current treatment regimes, is possible with PCNSL but this appears limited to patients less than 60 years of age at presentation (mostly patients less than 50 years of age).

1. Introduction

Over the last 30 years there has been an increasing interest in primary central nervous system lymphoma (PCNSL). This interest has increased rapidly over the last 10 years. Over this period of time there has been a change from the retrospective analysis of survival of relatively small numbers of patients with PCNSL treated by radiotherapy alone[1–3] to the development

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of prospective phase II studies investigating radiotherapy alone,[4] combined chemotherapy and radiotherapy or more recently chemotherapy alone (vide infra chemotherapy and radiotherapy sections). There has been some criticism expressed at International meetings that no large randomised phase III trial has been carried out in this disease. Only one small phase III trial of 53 patients has been published from the United Kingdom comparing whole brain radiotherapy (WBRT) alone with radiotherapy followed by chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone CHOP).[5] There is currently only one phase III trial, the German study G-PCNSL-SG-I in which after treatment with single agent methotrexate 4 g/m^2 those patients with a complete response (CR) are randomised between radiotherapy after completion of chemotherapy and radiotherapy delayed until relapse. In order to recruit enough randomised patients, those patients who do not achieve a CR are also randomised between immediate radiotherapy and cytarabine chemotherapy. These two groups will be combined for analysis.

The difficulty in carrying out a large trial is the rarity of the disease. The incidence of the disease has increased over the last 30 years, some of this increase has been due to acquired immunodeficiency syndrome (AIDS).[6–8] Excluding AIDS patients, the incidence is now nearly 10% that of gliomas.[8] The incidence has increased threefold in parallel with the increase in the incidence of non-Hodgkin's lymphoma. This increase has now levelled off over the last few years.[8] There has been a decrease in incidence in young patients and in those with AIDS because of highly active anti-retroviral treatment.[9] There has been no fall in the older immunocompetent population.[10] The increase in incidence is largely unexplained and not solely due to improved neuroimaging and stereotactic neurosurgery.[8] The annual number of patients is now three per million population (crude incidence rate). For Europe with a population of 731 million, there will be over 2000 patients per year with the disease. The median age is however 62 years and the incidence increases with increasing age. With the ageing population in Europe, more and more patients will be in their 70s and 80s. Many of these patients because of age, performance status and existing medical conditions will be excluded from phase III trials.[7] Not all cases of PCNSL will be diagnosed. Making the diagnosis depends on the awareness of Clinicians. Clinicians working in district hospitals rather than large hospitals with Cancer Centres may be less aware of multifocal, meningeal or ocular PCNSL. There is no doubt that since the introduction of stereotactic biopsy, rather than craniotomy, more elderly patients have been diagnosed with PCNSL. Some of these are only suitable for palliative treatment. Some patients are diagnosed by Neuroradiologists and thought not to be fit enough for stereotactic biopsy and confirmation by histology. When all patients diagnosed within a defined geographical area are included (rather than those recruited into a clinical trial), the overall survival is much worse.[7]

There is a general agreement that high dose methotrexate (MTX) with folinic acid rescue is the most active drug available currently for this disease.[11] Outside of clinical trials the standard approach is to use either high dose MTX with folinic acid rescue alone or in a combined chemotherapy regimen with well documented response rates and survival followed in either case by whole brain radiotherapy. In patients over 60 years of age, the dose of radiotherapy can be reduced or radiotherapy omitted if the risk of late neurotoxicity appears to be high.[12] Lymphoma specialists find it difficult to come to terms with using single agent chemotherapy for NHL, particularly when methotrexate is not included in the standard therapy for large B cell NHL viz. rituximab CHOP.[13] Until there is agreement on a combination chemotherapy regimen that could be tested against single agent methotrexate, there will not be a large randomised chemotherapy trial. More interest has been shown in randomising to immediate radiotherapy or radiotherapy until relapse after chemotherapy (e.g. G-PCNSL-SG-I). Lengthy discussions in the USA did not lead to a trial because with a CR rate of 66% over 600 patients would need to be treated with chemotherapy to produce over 400 patients for randomisation between radiotherapy and no radiotherapy.[12] Until new treatments emerge which will lead to phase III trials, we will have to use either the International Extranodal Lymphoma Study Group prognosis score[14] or the Nottingham/Barcelona prediction score to compare phase II trials.[15] These scores use the known prognostic factors of age, performance status, multifocal and/or meningeal disease or involvement of deep structures of the brain, CSF protein concentration and serum lactate dehydrogenase concentration.[14,15]

The other very important issue for PCNSL and indeed for brain tumours in general is the quality of life and cognitive function for survivors.[16] Survival with some motor impairment and mild short-term memory loss may be acceptable, but progressive severe cognitive deterioration resulting in long-term care without being able to recognise relatives may not be acceptable. The risk of this rises with increasing age (particularly those aged over 60 years).[17] Detailed neuropsychological evaluations are not readily available in every Cancer Centre and this has limited the amount of information available. In addition, there is no International agreement on which tests are the most useful. Many of these issues will be discussed at this workshop on PCNSL.

2. Biological and clinical aspects

The clinical presentation of PCNSL includes focal symptoms and raised intracranial pressure, similar to brain tumours in general but a key feature in PCNSL is the frequency of dementia in elderly patients. Seizures are less frequent that in other brain tumours because of the deep location of PCNSL in many patients. Spinal intramedullary lymphomas, primary leptomeningeal lymphomas, central neurogenic hyperventilation, pan-hypopituitarism and diabetes insipidus in spite of their rare occurrence represent other classical presentations of the disease. The most interesting feature, because it is more specific, is a uveitis present in 10–20% of patients at diagnosis. It must be carefully searched for by a slit lamp examination since it is asymptomatic in up to half of the cases. Systemic involvement is so rare at onset (<5%) that the need for extensive initial staging is debated; however, most authors recommend HIV testing, CT scanning of the thorax, abdomen and pelvis, craniospinal MRI scanning, CSF analysis and slit-lamp examination of the eyes, in addition to careful clinical examination.[18] CT and MRI typically show unifocal or multiple (1/3

of cases) periventricular, homogeneously enhancing lesions. The differential diagnosis of PCNSL includes mainly malignant gliomas and metastases. 'Ring-like' enhancement is very rare in immunocompetent patients and a HIV test is strongly advised in this situation. Atypical locations and/or aspects, such as non enhancing lesions, may lead to confusion with inflammatory or infectious-CNS disease (pseudo-tumoural multiple sclerosis, neurosarcoidosis, langerhans histiocytosis, acute disseminated encephalo-myelitis) or simulate other brain tumours (meningiomas, pituitary adenoma). Spontaneous (or steroid-induced) disappearance of the lesions is classic, hence the term 'ghost tumours'. However, the diagnosis is not PCNSL in all cases.[19]

The histopathological diagnosis is of malignant diffuse large B cell lymphomas (DLBCLs) in 90% of cases of PCNSL.[20] The detection of lymphoma cells in the CSF or in a vitreous biopsy when possible is sufficient to make the diagnosis without the need for a brain stereotactic biopsy. IL10 dosage[21] and detection of clonality by PCR techniques[22] may also represent helpful tools for the diagnosis. Recent studies have focused on rare pathological presentations. Although the large majority of PCNSL are of B origin, T cell lesions are occasionally seen. In the few series of the literature, the proportion of patients with T cell PCNSL is about 2–4% of cases. It was suggested that the T cell forms might be associated with a better prognosis. However, in a large retrospective study of 45 patients, the clinical presentation and outcome appear very similar to that of B cell PCNSL.[23] Primary low grade CNS lymphoma is another rare form, appearing in the literature as small series or single case reports. Among the low grade group, marginal zone lymphomas (mucosa-associated lymphoid tissue) represent the most common primary CNS lymphoma. Pathologically, these tumours demonstrate CD20+ CD3− small B lymphocytes with varying degrees of plasmacytic differentiation and predominantly k light chain restriction. It affects preferentially middle aged women (female to male ratio, 4:1), presents classically as dural-based masses mimicking meningioma and seems to be associated with a favourable clinical behaviour.[24]

The tumourigenesis of PCNSL is still poorly understood. In contrast to immunocompromised patients, the Epstein-Barr virus (EBV) does not appear to be involved in the pathogenesis of PCNSL in the immunocompetent population. The site of origin of the lymphoma cells, the biological mechanisms involved in the neoplastic transformation of lymphocytes and in their intriguing confinement within the CNS during the course of the disease in most cases remain obscure.[25] Primary DLBCL arising in the brain are morphologically indistinguishable from systemic forms and the WHO classification does not consider them as separate diseases. It remains therefore unclear whether the poor outcome of PCNSL compared to that of the systemic lymphomas is attributable to the specific cerebral environments and/or reflects an intrinsic aggressive biological behaviour. BCL 6 expression may predict improved survival but at the moment there is conflicting evidence from published studies.[26,27] While comparative genomic hybridisation analysis showed an overall similar chromosomal imbalance profile between PCNSL and extra-cerebral DLBCL,[28] there were differences such as the presence of an extremely high load of somatic mutations and an aberrant somatic hypermutation in several proto-oncogenes and tumour suppressor genes.[29] Distinct gene-expression signatures have been reported in systemic DLBCL investigated by lymphochip cDNA microarray and immuno tissue microarray, and associated with opposite outcomes: those with expression patterns similar to normal GC B cells (germinal center B-cell-like, or GCB) were associated with a significantly better overall outcome than those whose phenotypes resembled that of *in vitro*-activated peripheral blood cells (activated B-cell-like, or ABC).[30,31] Interestingly, in contrast with what has previously been postulated by several authors,[32,33] a recent study demonstrated a relatively homogeneous activated ABC immuno-phenotype of PCNSL providing new insights into interpreting the poor prognosis of PCNSL.[27]

3. The role of chemotherapy

The evaluation of new chemotherapy combinations against PCNSL in non-randomised trials has produced relatively small therapeutic progress. The use of divergent study designs and entry criteria as well as the presence of some methodological pitfalls leads to unreliable conclusions in single-arm prospective trials.[11] Some of the tested combinations include drugs without proven single agent activity; the drugs have been selected on their capacity to penetrate the blood–brain barrier (BBB) and on their efficacy against systemic lymphomas.

With current treatment, only a quarter or less of PCNSL patients survive more than 5 years, leading investigators to intensify therapeutic approaches to improve outcome. The indiscriminate use of intensified strategies, or combinations of strategies, is associated with increased neurological and systemic toxicity, which is a relevant issue considering that most patients are aged, with poor performance status. Therefore, a dilemma in PCNSL treatment is the choice between dose-intensified strategies to improve outcome versus deescalated approaches to avoid severe neurotoxicity.

3.1. *Conventional chemotherapy*

There is an unconfirmed consensus that combined chemo-radiotherapy is superior to radiotherapy alone.[11,34] This strategy is in accordance with therapeutic recommendations used for most of the localised aggressive lymphomas, where primary chemotherapy is followed by consolidation radiotherapy. High dose methotrexate (HD-MTX; dose $\geqslant 1\,g/m^2$) is the most effective drug against PCNSL;[11,35] it produces a response rate of 52–88% as monochemotherapy and 70–94% when used in combination. These chemotherapeutic approaches followed by WBRT are associated with a 2 year overall survival (OS) of 58–72% and 43–73%, respectively.[34,36–38] Several HD-MTX based combinations are being assessed in prospective trials. Currently, there is no proven benefit of additional drugs over HD-MTX alone except that HD-MTX alone without immediate radiotherapy afterwards appears to produce an inferior result.[39,40] Therefore, in ordinary clinical practice HD-MTX alone or combinations including this drug with well-documented efficacy should be used as primary approaches against PCNSL in both cases followed by WBRT.[12]

The efficacy of MTX depends on the duration of exposure and drug concentration,[41] which are determined by the administration schedule and pharmacokinetics. The optimal administration schedule for HD-MTX remains to be defined. The choice of the dose is a relevant issue considering that only 3% of the administered MTX will reach neural tissue. In fact, while standard dose MTX does not cross the BBB, doses 1–3 g/m^2 result in tumouricidal levels in the brain parenchyma and doses $\geqslant$3 g/m^2 yield tumoricidal levels in the cerebrospinal fluid (CSF). Infusion duration is strongly conditioned by the administered dose; in most trials using doses of 1–5 g/m^2, MTX has been administered in a 4 h infusion, while 24 h infusions have been used for higher doses. A significantly higher response rate and cerebrospinal fluid (CSF) levels have been obtained administering HD-MTX in a 3 h infusion.[42] Since MTX clearance from plasma is triphasic,[43] an initial rapid administration to overcome the distribution phase, followed by a more prolonged infusion, appears the most rational schedule.

Any regimen without HD-MTX is associated with the outcomes no better than with radiotherapy alone.[5,44,45] At least partially due to their poor BBB penetration, the most effective drugs against NHL, doxorubicin and cyclophosphamide, are associated with unsatisfactory results.[5,46] In spite of a good initial radiographic response, most patients treatment with CHOP or MACOP-B regimens experience relapse after 2–3 cycles. This may be explained by positive emission tomography (PET) studies that demonstrate early normalisation of the disrupted BBB, suggesting that the bulky tumour not protected by the BBB responds, while microscopic tumour is not adequately treated and progresses.[47] The use of these chemotherapy combinations should be avoided in the management of PCNSL.

3.2. *Chemotherapy 'sanctuaries'*

3.2.1. *Leptomeningeal lymphoma*

Meningeal treatment and prophylaxis is needed in PCNSL. This may be achieved by cranio-spinal radiation, high-dose systemic chemotherapy or by intrathecal chemotherapy. The first strategy is associated with increased myelotoxicity, while the indications and efficacy of the other two strategies are debatable. Preliminary data suggest that MTX doses $\geqslant$3 g/m^2 are associated with therapeutic concentrations in the CSF (10 μM) and eradication of meningeal disease.[48–50] Intrathecal administration produces drug levels 10-fold higher than those obtained with systemic chemotherapy, with more reliable CSF distribution when an intraventricular Ommaya reservoir is used.[48,51] MTX, cytarabine and steroids are the most commonly used drugs; a sustained release formulation of liposomal cytarabine for intrathecal injection is available and allows dosing once every 14 days.[52] More recently, anecdotal but encouraging results with intrathecal rituximab have been reported.[53]

The more widespread use of intrathecal chemotherapy has been limited by the fact that its efficacy in PCNSL patients has not been prospectively assessed and the addition of intrathecal chemotherapy seems not to improve outcome in patients who receive HD-MTX based chemotherapy.[11,54–56] Moreover, intrathecal chemotherapy is associated with increased risks of neurotoxicity and chemical meningitis as well as unacceptably high rates of infective complications in PCNSL patients treatment by using an Ommaya reservoir.[11,57]

Even if not routinely assessed, most of meningeal relapses seems to occur in patients with positive CSF cytology at diagnosis.[11,56] This has led some authorities to reserve intrathecal chemotherapy for patients with positive CSF cytology, with the aim of minimising toxicity.[45] However, leptomeningeal relapse is usually associated with brain recurrence, which constitutes the cardinal prognostic event in PCNSL, obscuring the effect of concurrent leptomeningeal relapse on survival, and, consequently, the potential benefit of intrathecal chemotherapy. Furthermore, the high local relapse rate observed in PCNSL patients indicates the inadequacy of primary chemotherapy and radiotherapy, and improvements in these strategies should be considered as priorities with respect to intrathecal therapy.[12]

3.2.2. *Intraocular lymphoma (IOL)*

Malignant lymphocytes involve the vitreous, retina and/or optic nerve, in isolation or as a component of more extensive PCNSL. Standard treatment against IOL remains to be defined. However there is no evidence in the literature to suggest that IOL should be treated in a different way from other presentations of PCNSL; only minor differences in the extent of RT fields and doses have been introduced in IOL series. Patients treated for IOL have an 80% risk of developing cerebral involvement after 10 years of follow up.

Chemotherapy efficacy against IOL is dependent on intraocular pharmacokinetics, which are not well understood. Pilot studies indicate that vitreous concentration of MTX following intravenous administration is 100-fold lower than serum.[58] Moreover, intraocular drug concentration is erratic, it is not predictive of response and it is lower in the vitreous humor, where lymphomatous cells usually grow, than in the aqueous humor.[58] As a consequence, ocular failure is common. Better disease control combining ocular irradiation with MTX based chemotherapy has been reported (see 'the role of radiotherapy').[59] Thus, the use of chemotherapy alone should be the subject of experimental protocols and not considered a standard approach in patients with IOL.

The above mentioned difficulties and the poor results obtained with conventional treatment have led investigators to search for new therapeutic strategies. Encouraging results in patients with recurrent or refractory IOL treated with high dose chemotherapy supported by autologous peripheral blood stem cell transplantation (APBSCT) have been reported.[60] However, this strategy has been associated with an increased incidence of neurotoxicity and mortality, especially in elderly patients. Some protocols using intavitreal injections of MTX, with or without thiotepa, have been associated with promising results and reduced morbidity,[61,62] suggesting that, if confirmed in future trials, intravitreal chemotherapy may become a valid alternative against IOL.

3.3. *Investigational strategies*

3.3.1. *Blood–brain barrier disruption*

Reversible BBB disruption (BBBD) by intra-arterial infusion of hypertonic mannitol followed by intra-arterial chemotherapy

is a strategy which leads to increased drug concentrations in the lymphoma-infiltrated brain and thus may improve survival. In institutions with adequate expertise, BBBD plus HD MTX has been associated with acceptable morbidity, high tumour response and survival rates, and only a 14% loss of cognitive function at one year.[63] In relapse patients, carboplatin-based chemotherapy and BBBD produced a 36% response rate, with a median duration of 6.8 months.[64] BBBD may prove most useful in the delivery of agents unlikely to traverse an intact BBB, such as unconjugated or radiolabelled monoclonal antibodies. However, this strategy is a procedurally intensive treatment, with vascular interventions, under general anaesthesia, monthly, over 1 year, and its role need further investigations in PCNSL.

3.3.2. *High-dose chemotherapy with APBSCT*

High-dose chemotherapy supported by APBSCT can be used to dose intensify chemotherapy as well as to replace WBRT in an effort to avoid treatment related neurotoxicity. Preliminary results indicate that this strategy is feasible in PCNSL patients. Activity data are, however, controversial because of the different induction and conditioning combinations used, which, as with conventional therapy, include drugs selected on the basis of their safety, efficacy against systemic lymphomas and ability to cross the BBB. In Germany,[65] induction with HD MTX, thiotepa and cytarabine followed by carmustine and thiotepa and hyperfractionated radiotherapy produced a 73% complete remission rate, with a 3% lethal toxicity rate, and a 3 year OS of 64%. Similar results have been reported by a Canadian group, using HD MTX followed by conditioning with thiotepa, busulfan and cyclophosphamide, without consolidation radiotherapy.[66] On the other hand, at the MSKCC,[67] MTX 3.5 g/m^2 followed by high dose cytarabine, and BEAM consolidation chemotherapy resulted in a significant proportion of relapses after transplant, with a median event-free survival of 9 months. The role of this strategy in PCNSL remains to be defined considering that the worldwide experience is still limited, and further studies will need to be done to identify the optimal induction and conditioning regimens. The lack of cross resistance with MTX has been an advantage when this strategy has been used as salvage therapy,[60] but it is possible that previously irradiated patients will have a higher risk of neurotoxicity.[60]

3.4. *Investigational drugs*

The small number of available active drugs limits further improvements in chemotherapy efficacy. It is important that patients with relapsed or refractory PCNSL should be entered onto a phases I/II trial assessing new active drugs and combinations. In fact, some active drugs have recently emerged from prospective and retrospective studies and are now being incorporated into ongoing phase II trials assessing new HD MTX-based combinations against PCNSL.

Temozolomide is an oral alkylating agent that spontaneously undergoes chemical conversion to MTIC (5-(3methyl-1-triazeno) imidaxole-4-carboxamide), resulting in 0–6 methylguanine-DNA methyltransferase depletion. This drug displayed excellent tolerability and a 26% response rate, mostly complete remissions, in a multicentre phase II trial on 23 patients with PCNSL relapsed or refractory to HD MTX.[68] Considering that it permeates the BBB, is well tolerated, even in elderly patients, and exhibits additive cytotoxic activity with radiotherapy, Temozolomide may be used as induction, maintenance or radiomimetic treatment against PCNSL. The latter application is supported by the positive experience on high grade gliomas; however, the sole experience with a radiomimetic in PCNSL patients (infusional 5 bromo-2′-deoxyuridine) has been associated with unacceptable neurotoxicity.[69] Preliminary data suggest that rituximab–temozolomide combination is well tolerated and active.[70,71]

Rituximab, a chimeric monoclonal antibody directed against the B cell specific antigen CD20, is an intriguing investigational drug. High doses of this drug can be safely infused to attain higher CSF concentrations.[72] Anecdotal experience with intravenous rituximab showed disappointing results,[73] while promising results have been reported in a few cases of leptomeningeal lymphoma treated with rituximab administered by the intraventricular route.[53] Duration of response, however, remains to be defined considering that treated patients died early due to intraparenchymal progression.

Topotecan, a camptothecin derivative that inhibits the enzyme topoisomerase I, produces an objective response in one third of patients with refractory or relapsed PCNSL, with a 1 year progression free survival of 13%.[74] Some retrospective evidence suggests a positive impact of the addition of high dose cytarabine to HD MTX.[11,75] The latter observation constitutes the primary end-point of one of the only two ongoing randomised trials in PCNSL.[76]

4. The role of radiotherapy

Radiotherapy alone has been the standard therapy for PCNSL for several years, producing a median survival of 12–26 months, a 5 year OS of 10–29%.[3–5,11,35,77–80] Despite the high complete remission (CR) rate, radiotherapy alone achieves disease control within the volume irradiated with doses up to 60 Gy in only 52–65% of cases,[4,81] and almost all patients relapse within a few months.

4.1. *Radiotherapy alone versus chemoradiation*

As discussed above, a widespread consensus supports the use of HD MTX containing chemotherapy followed by radiotherapy. However, owing to the absence of sound evidence from prospective randomised trials, the superiority of the combined strategy is not universally accepted and retrospective surveys reflecting therapeutic trends in ordinary clinical practice have shown that radiotherapy alone is usually only indicated in a minority (18–49%) of patients.[11,77,79,80]

4.2. *Consolidation radiotherapy parameters*

The optimal dose and volumes of post-chemotherapy irradiation have never been prospectively investigated. Doses between 20 and 50 Gy to whole brain (WB) with or without a tumour bed boost are currently used. A careful description of the pattern of failure after combined treatment modality would be useful to generate hypotheses on whether WB irradiation is really necessary or whether doses to be delivered to

WB and tumour bed could be different. Radiotherapy particularly when given with MTX is the main cause of neurotoxicity in PCNSL patients, mainly in patients over 60 years of age. Severe neurological impairment, dementia, brain atrophy, leukoencephalopathy have been reported in 5–83% of patients treated with chemoradiation.[11,16,34,38,82–87] In a significant proportion of cases, neurotoxicity was complicated by death. The concern raised by treatment-related late neurotoxicity led to the investigation of dose reduction and radiotherapy withdrawal in patients with a CR after chemotherapy. In fact, toxicity is dose and volume dependent[82,83,88–90] and no cognitive deficit versus a deficit of 27–31% was reported in PCNSL patients with WB doses of 30–36 Gy and of 37–45 Gy, respectively.[83,91] WB dose reduction from 45 Gy to 30.6 Gy in patients <60 years in CR after primary treatment increased the 3 year recurrence risk from 25% to 83% and decreased the 3 year OS from 92% to 60%.[83] However, these findings should be taken into account with caution due to their retrospective nature, the small subset of patients studied ($n = 25$), the concomitant reduction of dose to tumour bed from 55 to 30.6 Gy and the inclusion of patients whose CR was obtained by surgery, steroids or radiotherapy, which confound the estimation of the true effect of WB dose reduction in patients with CR after chemotherapy. Conversely, a critical analysis of the literature did not show any survival benefit with WB dose >40 Gy with respect to lower doses in patients with CR after primary chemotherapy.[75] Thus, the possibility to tailor the radiation dose and volume on the basis of response to chemotherapy should be prospectively explored. With regard to radiotherapy withdrawal, only data from single arm phase II trials, most of which are without any prospective cognitive function evaluation, are available. No firm conclusion can be reached from these trials.[39,50,58–95] In fact, a phase II trial is inadequate to support evidence-based guidelines and can only generate hypotheses and select treatment strategies to be tested in phase III trials. Comparisons of both survival and toxicity data from phase II trials are difficult because of an imbalance of prognostic factors amongst patients, department – (neurology versus others) or institution related selection bias, inhomogeneity in treatment variables, different and/or inadequate follow-up duration, and differences in study methodology. In fact conclusions on neurotoxicity are dependent on the definition used, the description of actuarial or crude survival, the baseline assessment of cognitive function, the neuropsychological assessment methods, ranging from clinical observation to mini-mental state examination to standardised psychometric methods, subset analyses, and the presence of co-morbidity or known predisposing factors.

4.3. *Radiotherapy withdrawal*

Taking all these limitations into account, a few considerations can be drawn. Radiotherapy alone yields a response rate of 60–97% as first line therapy[3–5,77] and 60–74% as salvage therapy.[40,91] Furthermore, in HD MTX based combination regimens, the CR rate was 33–58% after chemotherapy and 69–87% after radiotherapy.[34,36,38,83,97] Altogether, among patients who did not obtain a CR after primary chemotherapy, additional radiotherapy produced a complete response in 66% and a partial response in 12% of cases.[75] CR rate and median PFS were 82–88% and 32–40 months after single agent HD MTX followed by radiotherapy,[56,84] 30–65% and 13–17 months after single agent HD MTX without radiotherapy,[39,50,95] and 61% and 21 months with combination chemotherapy without radiotherapy.[57] Furthermore, a dose dependent positive survival benefit of consolidation radiotherapy was postulated.[83] Based on all these data, the contribution of radiotherapy against PCNSL appears evident. One of the basic principles of oncology is that a given treatment should produce a higher cure rate when the tumour volume is smaller.[98] Thus, consolidation radiotherapy against microscopic residual disease should be preferred to radiotherapy against more bulky disease at the time of failure, until proved otherwise. Moreover, among patients treated with upfront chemotherapy alone, 12–14% were unable to receive salvage treatment after failure,[57,75] and approximately a further 10% died of progressive disease during salvage radiotherapy.[91] Thus, about 1 in every 5 patients who receive chemotherapy alone as first line treatment would be deprived of the most active treatment against this disease but WBRT immediately after chemotherapy carries an increased risk of neurotoxicity. The risk with salvage radiotherapy could be greater than with radiotherapy given immediately after chemotherapy because patients would be older, have a poorer PS, and a larger tumour burden, which would require higher doses and larger volumes for a tumour bed boost.[40,56,84] Another argument in favour of the use of consolidation radiotherapy was the observation in one of the few series with adequate follow-up, that relapse within the first 2 years predicts an unfavourable outcome, thus stressing the strategic relevance of obtaining a durable CR with first line treatment. [97] However, WBRT as a salvage therapy after failure with initial MTX based chemotherapy can be associated with a substantial rate of response with a modest neurotoxicity rate if total radiation dose is less than 36 Gy.[91]

4.4. *Neurotoxicity from treatment*

The mechanisms underlying the development of neurotoxicity are poorly understood[99] and the wide range of reported neurotoxicities reflects the methodological flaws discussed above that hamper any reliable conclusion on the individual contribution of the several possible causes.

Radiotherapy is thought to play a key role in cognitive damage, since chemotherapy only regimens seem to achieve lower neurotoxicity rates. However, this comparison appears biased in favour of patients receiving chemotherapy alone, because in this case toxicity data refer only to patients with CR after chemotherapy, while the figure for patients receiving chemoradiation also includes partial responders or non-responders to chemotherapy who subsequently have a CR with WBRT.[100] Patients with CR and patients without CR could represent two different and non-comparable populations for many reasons. The disease itself contributes to the neurologic injury, due to widespread brain infiltration that causes cerebral scarring[87,101] and more rapidly growing tumours cause a greater neuropsychological impairment.[102] Late cognitive deficits maybe in part residual deficits due to the tumour itself as cognitive dysfunction is present in 83% of patients at the time of diagnosis and is improved only in 59% after CR to primary chemotherapy.[86] Patients with PCNSL who have

a partial response or no response to chemotherapy and then have a CR with radiotherapy may therefore experience greater cognitive dysfunction. In addition, these patients may be on cortico steroids for longer.[103] A neuropsychological baseline evaluation at completion of the treatment is recommended to assess the specific potential contribution of the tumour on cognitive dysfunction.

In general, cognitive disorders and dementia are age-related and their prevalence, which is 5–9% in the elderly general population[104,105] and 55% over 85 year,[106] confounds neurotoxicity assessment. However, the age related cognitive disorders in the elderly have a distinct presentation from those of delayed leukoencephalopathy, which is associated with typical subcortical impairment, psychomotor stammers, frontal syndrome, early ataxia and incontinence. The changes on MRI from baseline help to also distinguish leukoencephalopathy from age related neurodegenerative decline (Alzheimer's disease for example). Confounding factors in PCNSL are the occurrence of white matter dementia induced by lymphomatosis cerebri,[107] whose magnetic resonance imaging (MRI) findings may be indistinguishable from treatment related white matter damage[108,109] and the underestimation on MRI of the widespread microscopic infiltration by tumour cells throughout radiographically normal regions of the brain.[109] More widespread disease than expected from recent MRI scans may be found at autopsy.[109,110] Radiotherapy,[99,111–113] chemotherapeutic agents, and intrathecal chemotherapy[99,114–118] are all potentially neurotoxic and long-term cancer survivors treated with chemotherapy for non CNS tumours may experience persistent cognitive dysfunction.[104,119,120] However, the neurocognitive risk is increased in more than an additive way when treatments are combined[99,121] and the late neurotoxicity of chemotherapeutic agents in PCNSL is unknown. Careful consideration must be given as to whether radiotherapy is advisable after chemotherapy when a CR has been obtained with chemotherapy and the patient is older than 60 years of age and/or has significant cognitive deficit already.

4.5. *Strategies to reduce neurotoxicity*

The benefit of post-radiotherapy chemotherapy is uncertain and intrathecal chemotherapy has no impact on survival.[11,35,54,75] On the other hand, combination chemotherapy increased the risk of treatment related deaths with respect to single agent HD MTX from 0% to 3%[56,82,84] to 6–16%.[36,57,83,92,93,96] The penetration into CNS (and likely neurotoxicity as well) of chemotherapeutics administered after radiotherapy is facilitated due to the increased BBB permeability[122] and intrathecal chemotherapy increases the risk of neurotoxicity up to 40%,[123,124] particularly in patients with CSF flow abnormalities, which are very frequent in PCNSL. Therefore, the selection of the timing of the therapeutic modality sequence, and the drugs to be included in first line regimens with HD MTX should be driven by prospective assessment through well-designed trials of agents active against PCNSL rather than by empiricism. Furthermore, neurotoxicity should be prospectively assessed with appropriated tests as there are risks from drawing conclusions from poorly designed studies.

Therapeutic results with chemoradiation are unsatisfactory as 5 year OS remains poor and the quest to find a more effective first line treatment remains the main challenge for PCNSL research. However, quality of life and treatment toxicity should also be optimised. Among possible areas of investigation, priority should be given to the individualisation of the patho-physiological mechanisms of neurotoxicity and of risk factors, such that neuroprotective or rehabilitative therapies can be used to prevent or treat cognitive deficits. The relevance of polymorphisms of methionine metabolism[125] and of hereditary defects leading to S-adenosylmethionine (SAM) deficiency and brain demyelination[126] in the pathogenesis of neurotoxicity has been reported. Among potential candidates for experimentations on treatment of cognitive deficit are SAM supplementation,[126] dextromethorphan,[127] methylphenidate,[128] aminophylline and high dose folinic acid,[129] and cognitive rehabilitation.[130]

5. Discussion

The discussants with the authors were: Dr. Antonio Omuro, Hopital Pitie-Salpetriere, Paris, France; Peter O'Brien, Newcastle Mater Hospital, Australia; Dr. Lucien A Nedzi, Tulane University, New Orleans, USA.

Topics discussed:

- Staging and response criteria.
- Single agent high dose methotrexate (HD-MTX) chemotherapy or combination chemotherapy including HD-MTX.
- Dose of radiotherapy and planning treatment volume. Radiation dose in patients >60 years of age.
- Late neurological sequelae and psychiatric problems in patients with PCNSL – Informed consent for treatment.
- Long-term survival.

5.1. *Staging and response criteria*

Reference was made to the International Workshop of the International PCNSL Collaboration Group.[18] It was suggested that all clinical investigators in the field should attempt to follow these guidelines.

5.2. *Single agent high dose methotrexate (HD-MTX) chemotherapy or combination chemotherapy including HD-MTX*

Although combination chemotherapy such as rituximab CHOP is standard therapy for large B cell NHL at nodal and other extranodal sites, there is no combination regimen that includes HD-MTX which has been accepted internationally. In a multi-variate analysis of 288 patients treated with chemotherapy containing HD-MTX (>1 g/m^2) with or without radiotherapy, high dose cytarabine improved overall survival if given with HD-MTX (>3 g/m^2) (preferably after MTX rather than before).[75] The role of cytarabine after MTX compared with MTX alone is being addressed in a randomised phase II study of the International Extranodal Study Group (IELSG # 20 trial).[76] HD-MTX or combinations with well-documented efficacy should be given and followed with radiotherapy in or-

dinary clinical practice (outside of clinical trials). HD-MTX alone without radiotherapy should at the moment be considered to be experimental.[39,40]

5.3. *Dose of radiotherapy and planning treatment volume: radiation dose in patients >60 years of age*

The planning treatment volume for radiotherapy should include the whole brain and the eyes and optic nerves (shielding the anterior chamber and lens). Involved field radiotherapy is insufficient.[81] The whole brain dose in IELSG # 20 is 30–36 Gy in 15–20 fractions over 3–4 weeks with a 9–10 Gy in five fractions in 1 week involving field boost in patients <60 years of age. In the G-PCNSL-SGI protocol, the whole brain dose is 45 Gy in 30 fractions over 6 weeks. In patients >60 years of age, clinical judgment is needed. Patients who have significant dementia (as judged by the mini mental state examination) and have had a complete response to chemotherapy should not receive whole brain radiotherapy. Patients who have no significant dementia could receive a lower dose of whole brain radiotherapy, for example, 30.6 Gy in 17 fractions over 4 weeks[83] which might reduce the risk of late neurotoxicity in this age group. Alternatively radiotherapy could be omitted if the patient has received adequate chemotherapy (a combination regimen). Patients who have only a partial response of their disease could receive lower dose radiotherapy or second-line chemotherapy.

5.4. *Late neurological sequelae and psychiatric problems in patients with PCNSL: informed consent for treatment*

Acute psychiatric episodes are unusual in patients >60 years of age, progressive dementia is more common. Involvement of a psychogeriatrician is useful in the management of these patients. Written information on the risk of dementia is essential to obtain informed consent.

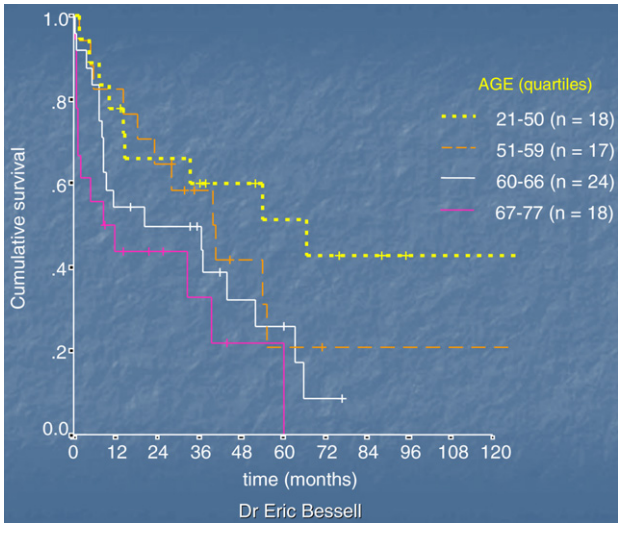

Fig. 1 – The overall survival of 77 patients with PCNSL treated either with BVAM or CHOD/BVAM chemotherapy followed by radiotherapy. Survival according to age (quantities) and implies censored observation.

5.5. *Long-term survival*

The long-term survival of 77 patients treated with the BVAM or CHOD/BVAM regimen followed by whole brain radiotherapy was shown (Fig. 1). The 10 year overall survival of patients under 60 years of age was 32.4% (95% C.I. 14.1–50.8) with no long-term survivors aged over 60 years at diagnosis.[15] Similar long-term cause-specific survival has been shown from the Memorial Sloan Kettering Cancer Center, New York, USA.[85] More long-term follow-up is needed from published prospective series.

Conflict of interest statement

All of the authors have no conflict of interest in any of the statements made in this workshop report (Reprinted with permission from Elsevier from Bessell et al.[15]).

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