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CLINICAL STUDY – PATIENT STUDY

Increasing age at diagnosis and worsening renal function in patients with primary central nervous system lymphoma

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Abstract High-dose Methotrexate (MTX) is the most useful cytotoxic drug used in the treatment of primary central nervous system lymphoma (PCNSL). Dose reduction should be made in patients with reduced renal function. We evaluated the age of patients over a period of 22 years and estimated their glomerular filtration rate. One hundred and two patients were treated in Nottingham University Hospitals (a regional centre for neurosurgery) during the period 1986–2008. Patients were treated either with the BVAM regimen (carmustine, vincristine, cytarabine, MTX) or with CHOD (cyclophosphamide, doxorubicin, vincristine and dexamethasone) given for one cycle prior to BVAM. The age at which patients were diagnosed with PCNSL increased during the period of the study. During the first half of the study period (1986–1997) the median age was 60.5 years, compared to a median age of 65 years during the second half of the study period (1998–2008) ($P = 0.001$). The estimated glomerular filtration rate decreased with age over 40 years in a similar way to the general population. The increasing age of patients with PCNSL and decreasing renal function limit the intensity of chemotherapy with MTX containing regimens.

Keywords Primary central nervous system lymphoma · Renal function · Age · Methotrexate

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Introduction

Age over 60 years is an adverse prognostic factor [1–3] for patients with primary central nervous system lymphoma (PCNSL) as it is for large B-cell non-Hodgkin's lymphoma in general [4]. In earlier series of patients with PCNSL the median age was 55–60 years of age [5, 6]. With the ageing population and the increasing safety of stereotactic biopsy the median age has increased with only a minority of patients being less than 60 years of age [7]. Renal function does not start to deteriorate in the general population until the age of 40 years and steadily decreases with age after that[8].

High dose Methotrexate (MTX) is the most useful cytotoxic drug in the treatment of PCNSL. As a single agent it is given at a dose of 4–8 g/m^2 with folinic acid [9, 10] or at a dose of 1.5–3.5 g/m^2 in combination with cytarabine or other cytotoxic drugs [11, 12]. There is general agreement that high dose MTX can be given in patients over the age of 60 years but that dose reduction should be made and the creatinine clearance should be calculated prior to each treatment with MTX [13]. We calculated the estimated glomerular filtration rate (eGFR) for a large single centre series of 102 patients to determine how renal function changes with age in this patient population.

Patients and methods

Patients

All these patients had histologically proven PCNSL almost all by stereotactic biopsy. None of these patients had evidence of HIV infection or positive HIV serology. Patients

with PCNSL after organ transplantation were excluded from this series.

A total of 102 patients were seen between 1986 and 2008 and were all referred to E.M.B. The age of all the patients was known and the estimated glomerular filtration rate could be calculated for 92 patients using the Cockcroft-Gault formula. Sixty one patients were male and forty one patients were female.

Results

The median age at diagnosis for the study population as a whole was 64 years. During the first half of the study period (1986–1997) the median age at diagnosis was 60.5 years ($n = 32$). During the second half of the study period the median age at diagnosis was 65.0 years ($n = 60$). Using the Wilcoxon rank sum test, the difference in median age at diagnosis between the first and second halves of the study period was found to be statistically significant, $P = 0.001$. The difference in age at diagnosis between the first and second halves of the study period is illustrated in Fig. 1.

The variation in eGFR with age is shown in Fig. 2. The plotted values are superimposed on the mean ^{51}Cr-ETDA GFR measurements ± two standard deviations obtained from 428 subjects who were being assessed as potential live kidney donors (age range 19–72)[8]. This plot shows that the eGFR obtained for 92 patients with PCNSL fall almost entirely within the median rang ± two standard deviations.

Patients with PCNSL have therefore similar renal function to the general population.

88 patients had an eGFR > 50 ml/min. Of these, 23 patients had an eGFR > 100 ml/min. 4 patients had an eGFR < 50 ml/min (40, 42, 46, and 49 ml/min). Two of these patients completed BVAM chemotherapy and two patients received only carmustine (BCNU).

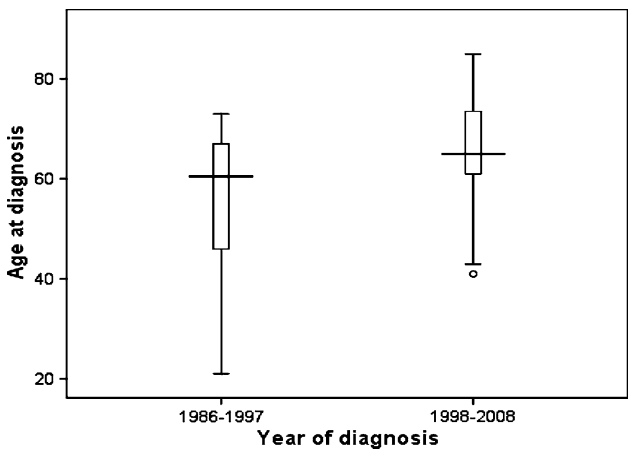

Fig. 1 Age at diagnosis during the first and second halves of the study period

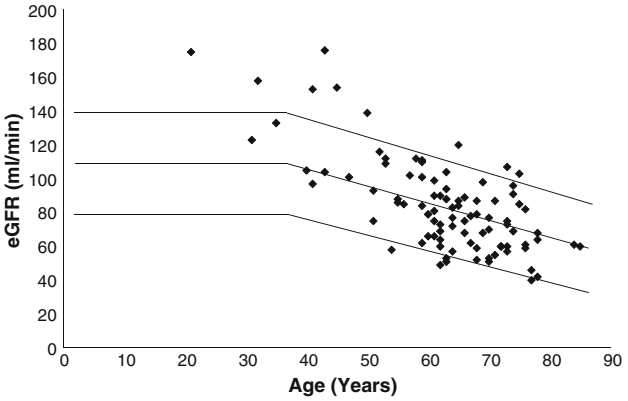

Fig. 2 The solid lines show the mean glomerular filtration rate ± two standard deviations for a normal population of potential live renal transplant donors [8]. The plotted points are the eGFR of 92 patients with PCNSL according to their age

Discussion

It is well known that the incidence of PCNSL increases with increasing age. It has also been shown that the incidence rate of PCNSL increased steadily from the 1970s to a peak in the mid-1990s [14, 15]. This increase in incidence rate could not be explained by developments in diagnostic imaging and the introduction of new neurosurgical procedures such as stereotactic biopsy [14].

This case series shows for the first time that the median age of diagnosis of PCNSL has increased over the last 20 years. This is likely to be explained in part by an increase in the median age of the population as a whole.

The renal function of patients with PCNSL in this series was similar to that of the normal population [8] (428 live kidney donors). The GFR remains constant until the age of 40 years and then declines at a rate of 9.1 ml/min/1.73 m^2 per decade. This series also shows that the age of the patients at diagnosis is increasing and therefore renal function at diagnosis will be decreasing. If the dose of MTX administered is reduced in patients with poor renal function it follows that the dose of MTX that can be given will continue to decrease in the future. Of the patients treated recently (2000–2008) only 14% are aged less than 60 years.

The largest randomised controlled trial of chemotherapy involving high dose MTX has been conducted by the German primary CNS lymphoma study group [13]. In this study the dose of MTX given as a single agent was 4 g/m^2 given with folinic acid rescue every 2 weeks. Patients with a creatinine clearance of <50 ml/min were excluded from

the study. High dose MTX is in general not safe to give to patients with a creatinine clearance of <50 ml/min. Patients with creatinine clearance of ≥100 ml/min received the full dose. Patients with a creatinine clearance of 80 ml/min received 80% of the dose (3.2 g/m^2) and patients with a creatinine clearance of 60 ml/min received a dose of 2.4 g/m^2 and patients with a creatinine clearance of 50 ml/min received 2 g/m^2. The MTX dose was therefore reduced in 18% of patients ≤60 years, in 44% of patients >60 years and 70% of those aged >70 years. The mean dose reduction was 15.6%. If dose reduction is not carried out according to creatinine clearance renal toxicity occurs in 40% of all cycles of HDMTX (8 g/m^2) [14].

In the BVAM and CHOD BVAM regimes the MTX dose has been 1.5 g/m^2 over 4 h with folinic acid rescue. Patients with an eGFR of <50 ml/min were generally not treated with high dose MTX although four patients in this series were. Only 25% of patients in this series had an eGFR of ≥100 ml/min so if higher doses of MTX had been used 75% of patients would have required a dose reduction with the first cycle.

The median age of patients with PCNSL is increasing and although the renal function of these patients is similar to the normal population adjustment of the MTX dose would have to be made in the majority of patients either if single agent doses of 4–8 g/m^2 are used or doses of 1.5–3.5 g/m^2 are used in combination with other cytotoxic drugs such as cytarabine.

References

1. Ferreri AJM, Blay J-Y, Reni M et al (2003) Prognostic scoring system for primary CNS lymphomas: the international extranodal lymphoma study group experience. J Clin Oncol 21:266–272
2. Bessell EM, Graus F, Lopez-Guillermo A et al (2004) Primary non-Hodgkin's lymphoma of the CNS treated with CHOD/BVAM or BVAM chemotherapy before radiotherapy: long term survival and prognosis factors. Int J Radiat Oncol Biol Phys 59:501–508
3. Abrey LE, Ben-Porat L, Panageas KS et al (2006) Primary central nervous system lymphoma: the memorial Sloan-Kettering Cancer Centre prognostic model. J Clin Oncol 24:5711–5715
4. Anonymous: the international non-Hodgkin's lymphoma prognostic factors project (1993) A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987–994
5. De Angelis LM, Yahalom J, Heinemann M-H et al (1990) Primary CNS lymphoma: combined treatment with chemotherapy and radiotherapy. Neurology 40:80–86
6. Bessell EM, Punt J, Firth J et al (1991) Primary non-Hodgkin's lymphoma of the CNS: phase II study of chemotherapy (BVAM) prior to radiotherapy. Clin Oncol 3:193–198
7. Bessell EM, Hoang-Xuan K, Ferreri AJ et al (2007) Primary central nervous system lymphoma: biological aspects and controversies in management. Eur J Cancer 43:1141–1152
8. Grewal GS, Blake GM (2005) Reference data for 51 Cr-EDTA measurements of the glomerular filtration rates derived from live kidney donors. Nucl Med Commun 26:61–65
9. Batchelor T, Carson K, O'Neill A et al (2003) Treatment of primary CNJ lymphoma with Methotrexate and deferred radiotherapy: a report of NABTT 96–07. J Clin Oncol 21:1044–1049
10. Herrlinger U, Kuker W, Uhi M et al (2005) NOA-03 trial of high-dose Methotrexate in primary central nervous system lymphoma: final report. Ann Neurol 57:843–847
11. Ferreri AJ, Foppoli M, Martelli M et al. (2008) Randomised phase II trial on primary chemotherapy with high-dose Methotrexate alone or associated with high-dose cytarabine for patients with primary central nervous system lymphoma. Ann Oncol 19(4), abst. 065
12. Omuro AM, Abrey LE (2006) Chemotherapy for primary central nervous system lymphoma. Neurosurg Focus 21:E12
13. Jahnke K, Korfee A, Martus P et al (2005) High-dose Methotrexate toxicity in elderly patients with primary central nervous system lymphoma. Ann Oncol 16:445–449
14. Olson JE, Janney CA, Rao RD, Cerhan JR et al (2002) The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. Cancer 95(7):1504–1510
15. Kadan-Lottick NS, Skluzacek MC, Gurney JG (2002) Decreasing incidence rates of primary central nervous system lymphoma. Cancer 95(1):193–202