

Effect of high dose cytosine arabinoside on quantitative EEG in patients with acute myeloid leukemia

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Received: 20 July 2015 / Accepted: 23 December 2015 / Published online: 13 January 2016
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Abstract Background EEG activity is considered an index of functional state of brain. Chemotherapy (CT), used for non-central nervous system (CNS) cancer, can cross the blood brain barrier and contribute to changes in the functional state of brain that can alter background EEG activity. Quantitative EEG (qEEG) is superior to conventional EEG in the detection of subtle alterations of EEG background activity and for this reason, the use of qEEG might assist the clinician in evaluating the possible effect of CT on the CNS. The nucleoside analog cytosine arabinoside (Ara-C) is one of the milestone chemotherapeutic agents used for treatment of acute myeloid leukemia (AML). Our observational study evaluates the possible effect of Ara-C on the qEEG of patients with AML, without CNS involvement. We conducted an observational study on newly diagnosed AML patients without CNS involvement, undergoing treatment with Ara-C to analyze the possible effect of Ara-C high doses on EEG background activity using qEEG analyses. A total of nine AML patients, 5 with Ara-C i.v. high dose (≥ 3 g/m² die), 4 with standard dose (100 mg/m² die) underwent qEEG (at rest, during hyperpnoea, mental arithmetic task and blocking reaction). We compared the EEG background activity of

the two groups at baseline and after 6 months. Statistical analysis showed no significant differences between the two groups in mean relative power for all frequency bands, at rest and during hyperpnoea, mental arithmetic task and blocking reaction. Our data indicate that high dose Ara-C i.v. did not induce significant changes on EEG background activity in our patients. Future research in this area could include prospective studies that would combine qEEG and neuropsychological testing to assess the impact of CT on brain functions.

Keywords High dose cytosine arabinoside · CNS · qEEG · Acute myeloid leukemia

Introduction

The EEG is rich in information on cortical, neuronal activity in the brain and an appropriate signal processing will give valuable information on the brain activity which could not be obtained by other imaging tools (Musha et al. 2004). A number of studies have confirmed that quantitative EEG (qEEG) analyses are far superior to conventional EEG in the detection of subtle alterations of EEG background activity (John 1989; Fitz-Gerald and Patrick 1991); they reflect the time course of pharmacologic effects of a drug and provide an independent measure of bioavailability in the CNS (Knott 2000).

Chemotherapy (CT) used for non-central nervous system cancer may lead to changes in EEG frequency and EEG slowing is widely considered as an indicator of central nervous system dysfunction (CNS); therefore, it appears that the inclusion of qEEG measures might provide valuable, additional information concerning possible pharmacological impact on the CNS (Cho et al. 2012; Clemens

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et al. 2006; Veauthier et al. 2009). Background EEG activity, in particular, represents the functional state of the brain (Cho et al. 2012; Knott 2000) and for this reason, the use of qEEG can assist the clinician in investigating and evaluating the effect of CT on the CNS (Ueberall et al. 1996).

Of the systemic chemotherapies used for treatment of acute myeloid leukemia (AML), the nucleoside analog Ara-C is one of the milestone chemotherapeutic agents. It can be administered both at standard low doses and high-doses, as induction or consolidation therapy. For younger AML patients (aged 18–60 years) an induction treatment based on the combination of Ara-C and anthracyclines is universally considered the standard of care. Ara-C is generally given intravenously in conventional dose (100 mg/m²/daily), but some induction regimens provide for the use of high-dose (≥ 2 g/m²/daily) administration (Russo et al. 2005; Willemze et al. 2014).

At conventional dose, Ara-C crosses the blood–brain barrier (BBB) poorly with blood–cerebrospinal fluid (CSF) transport occurring by facilitated diffusion across the choroid plexus. However, high-dose Ara-C i.v., yields higher levels in the CNS and its concentration in CSF reaches 6–22 % of plasma values. While standard intravenous doses of Ara-C are rarely associated with neurotoxicity, high intravenous dose of the drug has been noted to produce a number of CNS alterations, the most common of which are acute or subacute symmetric pancerebellar syndrome, sometimes associated with seizures and coma (Lazarus et al. 1981).

Given that (1) EEG background activity can be an index of the functional state of brain (2) the use of quantitative EEG is considered optimal for detecting subtle alterations in EEG background activity (3) AraC can cross the BBB and could lead to changes in EEG frequency, we conducted an observational study on patients with newly diagnosed AML, without CNS involvement, undergoing treatment with Ara-C to analyze the possible effect of high doses of Ara-C on EEG background activity using qEEG analyses.

We studied nine patients with newly diagnosed AML (four male and five female with a median age of 49 years, range 38–64) before and after 6 months of treatment, comparing patients treated with standard and high Ara-C doses; all patients underwent induction treatment at our institution. This study was approved by Ethical Committee of our Institute.

All patients were studied for CNS involvement at diagnosis with CNS imaging and diagnostic lumbar puncture: no cases of CNS leukemia involvement were diagnosed. AML patients with preexisting organic or psychiatric disorders and patients treated with drugs potentially interfering with the CNS (other than Ara-C) were excluded. Overall, four patients were treated with induction chemotherapy containing standard dose of Ara-C (100 mg/m²/daily in continuous infusion for 10 days)

whereas five patients were treated with high-dose Ara-C (3 g/m²/12 h during days one, three, five and seven in two cases (Willemze et al. 2014) and 2 g/m²/daily for five consecutive days in the remaining three patients) (Russo et al. 2005). All patients underwent an electroencephalographic evaluation before and after 6 months of treatment with Ara-C i.v. For electroencephalographic evaluation, we used an EEG machine MICROMEDIA BQ2400 Studio ACQDV to 25 channels.

Nineteen scalp-electrodes were placed according to 10–20 International System: eyes movements, electromyographic activity and electrocardiogram were recorded via additional skin surface electrodes. Electrode impedance was maintained below 20 k Ω . Filters were set at 1.6 and 70 Hz, and signal was notch filtered. All EEG recordings were acquired with a 256 bit sampling rate. Recording sessions included: 10 min at rest with eyes closed (REST), 5 min during hyperpnoea (HP), 5 min during opening and closing eyes (BR) and 5 min during mental arithmetic task (MA) which consisted of continuous subtraction of the same digit from an initial starting number. EEG was always recorded in a silent room at the same time of day, constantly controlling the patient's state of alertness by evaluation of EEG alpha

Table 1 Comparison of the mean relative power between baseline and 6 months of follow-up, for all frequency bands in the different tasks

| | Baseline Mean \pm SD | 6 months Mean \pm SD | Wilcoxon test <i>p</i> value |
|-----------------|---------------------------|---------------------------|---------------------------------|
| Frequency bands | | | |
| Rest | | | |
| Delta | 24.40 \pm 28.42 | 27.89 \pm 32.84 | 0.678 |
| Theta | 29.44 \pm 39.07 | 22.60 \pm 22.68 | 0.767 |
| Alpha | 83.99 \pm 116.49 | 66.99 \pm 72.35 | 0.767 |
| Beta | 14.01 \pm 7.22 | 18.17 \pm 9.38 | 0.374 |
| MA | | | |
| Delta | 23.62 \pm 13.61 | 31.92 \pm 31.96 | 0.859 |
| Theta | 21.17 \pm 25.04 | 25.03 \pm 29.64 | 0.953 |
| Alpha | 47.87 \pm 53.53 | 43.21 \pm 30.95 | 0.859 |
| Beta | 12.90 \pm 5.54 | 18.58 \pm 6.92 | 0.086 |
| HP | | | |
| Delta | 26.39 \pm 24.82 | 110.44 \pm 208.11 | 0.859 |
| Theta | 31.54 \pm 43.18 | 38.05 \pm 40.63 | 0.678 |
| Alpha | 48.11 \pm 53.66 | 68.81 \pm 69.98 | 0.086 |
| Beta | 13.51 \pm 6.23 | 21.95 \pm 12.70 | 0.214 |
| BR | | | |
| Delta | 73.75 \pm 65.75 | 74.23 \pm 65.57 | 0.110 |
| Theta | 22.83 \pm 22.86 | 22.08 \pm 17.64 | 0.767 |
| Alpha | 30.55 \pm 40.99 | 28.48 \pm 24.90 | 0.767 |
| Beta | 10.88 \pm 4.58 | 16.74 \pm 6.51 | 0.139 |

MA mental arithmetic task, HP hyperpnoea, BR opening and closing eyes

Table 2 Comparison of the mean relative power at baseline and 6 months of follow-up between high and low dose groups, for all frequency bands in the different tasks

| Frequency band | Baseline | | | At 6 months | | |
|----------------|--|---|--|--|---|---|
| | High dose (5 patients) Mean \pm SD | Low dose (4 patients) Mean \pm SD | Mann–Whitney test <i>p</i> value | High dose (5 patients) Mean \pm SD | Low dose (4 patients) Mean \pm SD | Mann– Whitney test <i>p</i> value |
| REST | | | | | | |
| Delta | 35.97 \pm 35.09 | 9.93 \pm 3.15 | 0.111 | 30.61 \pm 43.27 | 24.49 \pm 18.73 | 0.905 |
| Theta | 44.33 \pm 48.60 | 10.82 \pm 9.52 | 0.556 | 28.06 \pm 29.84 | 15.77 \pm 8.51 | 0.999 |
| Alpha | 111.41 \pm 152.52 | 49.71 \pm 48.53 | 0.730 | 67.09 \pm 83.80 | 66.87 \pm 67.80 | 0.999 |
| Beta | 16.11 \pm 8.29 | 11.38 \pm 5.55 | 0.556 | 19.17 \pm 11.38 | 16.92 \pm 7.64 | 0.999 |
| MA | | | | | | |
| Delta | 18.98 \pm 9.10 | 29.42 \pm 17.40 | 0.286 | 36.05 \pm 40.46 | 26.76 \pm 21.85 | 0.730 |
| Theta | 28.51 \pm 32.78 | 12.00 \pm 6.16 | 0.999 | 32.37 \pm 38.43 | 15.86 \pm 13.09 | 0.730 |
| Alpha | 63.96 \pm 68.93 | 27.75 \pm 18.28 | 0.999 | 39.61 \pm 27.75 | 47.71 \pm 38.47 | 0.905 |
| Beta | 13.14 \pm 5.96 | 12.61 \pm 5.86 | 0.999 | 18.23 \pm 6.35 | 19.02 \pm 8.58 | 0.905 |
| HP | | | | | | |
| Delta | 32.65 \pm 31.76 | 18.56 \pm 12.29 | 0.413 | 55.92 \pm 83.58 | 178.58 \pm 308.28 | 0.413 |
| Theta | 44.52 \pm 56.57 | 15.31 \pm 8.60 | 0.730 | 50.28 \pm 52.20 | 22.76 \pm 14.40 | 0.730 |
| Alpha | 59.33 \pm 65.72 | 34.10 \pm 38.04 | 0.556 | 72.90 \pm 92.96 | 63.71 \pm 38.42 | 0.730 |
| Beta | 13.41 \pm 6.79 | 13.64 \pm 6.47 | 0.999 | 18.90 \pm 11.08 | 25.77 \pm 15.22 | 0.556 |
| BR | | | | | | |
| Delta | 92.04 \pm 86.65 | 50.89 \pm 16.25 | 0.999 | 104.18 \pm 76.14 | 36.79 \pm 19.27 | 0.413 |
| Theta | 20.49 \pm 16.96 | 25.76 \pm 31.45 | 0.999 | 27.75 \pm 22.16 | 15.00 \pm 7.39 | 0.413 |
| Alpha | 13.06 \pm 6.67 | 52.42 \pm 57.21 | 0.730 | 20.85 \pm 12.05 | 38.01 \pm 35.23 | 0.905 |
| Beta | 10.22 \pm 3.84 | 11.71 \pm 5.89 | 0.905 | 18.73 \pm 6.97 | 14.25 \pm 5.79 | 0.413 |

MA mental arithmetic task, HP hyperpnoea, BR opening and closing eyes

rhythm. The off-line spectral analysis was performed using the Fast Fourier Transform on 5–10 min of EEG signal, manually segmented into ≥ 2 s epochs, after visual elimination of ictal and/or interictal abnormalities, movements artifacts, eye-blinking, muscle activity or drowsiness. These epochs were collected for each frequency band: delta [1–3.5] Hz; theta [4–7] Hz; alpha [8–12.5] Hz and beta [13–30] Hz. Relative power values were considered due to their lower inter-subject variability (Nuwer 1988).

We used the Wilcoxon test to compare the mean relative power of the EEG background activity at baseline and at 6th month follow-up, for all nine patients, for all frequency bands in the different tasks (REST, HP, MA, BR).

Then we also applied the Mann–Whitney test to compare the mean relative power for all frequency bands at REST and during HP, BR, MA, between the two groups (i.e. standard and high-doses Ara-C) separately at baseline and at 6th month follow-up.

No significant differences in the mean relative power were observed between baseline and 6th month follow-up in all patients (nine patients), for all frequency bands in the different tasks (Table 1).

No significant differences in the mean relative power for all frequency bands in the different tasks were observed between the two groups, either at baseline or at final follow-up (Table 2).

No patients developed any clinical signs of CNS toxicity during induction treatment. Patients were followed in a monthly visit during the clinical observation period and a neuroradiological examination was performed for each patient at final follow-up, which indicated no CNS involvement.

Discussion

Though there have been numerous published studies regarding EEG changes in patients on CT treatment for non central system cancer, the majority of these reports have involved conventional EEG (Sainio et al. 1989; Korinthenberg et al. 2002). A few studies have been published using qEEG to investigate therapy-related CNS side effects of antileukemic treatment, but they were concerning children suffering from acute lymphoblastic leukemia (ALL) (Ueberall et al. 1996).

Since drugs are among the more powerful influences that alter brain rhythms (Knott 2000), in this study we used qEEG analyses for patients with AML, undergoing treatment with Ara-C; the choice to use qEEG is in line with previous reports that have confirmed that qEEG analyses are far superior to conventional EEG in the detection of subtle alterations of background activity (John 1989; Fitz-Gerald and Patrick 1991). Our data showed no significant changes in EEG background activity after 6 months of treatment with Ara-C i.v., either in standard or high doses. These results indicate that screening patients who are receiving Ara-C, to detect possible therapy-related CNS side effects before clinical symptoms appear, could be done utilizing this method. Future studies should have a longer follow-up. In addition, a larger sample size will be necessary to confirm our results in this particular patient population. Quantitative EEG offers a promising approach for the study of therapy-induced CNS side effects of CT. Furthermore, literature data indicates that neuropsychological testing is the current preferred method of examining the impact of CT on cognitive functions (Kadan-Lottick et al. 2009; Moleski 2000).

Taking this into consideration, future research in this area could include prospective studies that would combine qEEG and neuropsychological testing to assess the impact of CT on brain functions (Cho et al. 2012). Lastly, this study suggests that a collaborative approach where different specialists closely monitor a drug's effects could benefit the clinician who wants to use a potentially neurotoxic chemotherapy carefully.

Acknowledgments The Authors wish to thank Ms. Lesley Pritikin for reviewing the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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