Chemobrain in patients participating in clinical trials

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Background:
The observation that cytotoxic drugs given systemically for non-CNS tumors might have neurotoxic effects on cognitive functioning was made decades ago. Cancer patients have benefited from the introduction of new drugs and treatment regimens in survival and quality of life but participation in clinical trials remains low.
Professional oncology organisations encourage participation in clinical trials as a routine component of cancer care but only 2-10% of cancer patients participate. There are many patient's, clinician's and other factors for poor participation in clinical trials but chemobrain factor and other cognitive impairments are less explored as potential barrier. Recent studies have shown that older age and lower cognitive reserve but also genetic factors may play a role in increasing susceptibility to cognitive dysfunction such as associations with apolipoprotein E and catechol-O-methyltransferase. A variety of research definitions for mild cognitive impairment are in place, but there is no consensus on the optimal definition.
The term chemobrain or chemotherapy-induced cognitive impairment is recognized as a common adverse effect of chemotherapy.
In the past years, the number of clinical trials has increased rapidly in Croatia and the actual degree of understanding or perceptions of clinical trial participating is unknown.
Aim of this study is to evaluate whether patients which signed informed consent to participate in clinical trials (both, academic and sponsored) have different chemobrain status than other.

Methods:
Adult cancer patients receiving chemotherapy in General Hospital Pula between January 2010 and December 2012. In experimental arm were 32 adult patients with advanced cancer (stage IV), ECOG PS 0-3, without CNS involvement which have signed clinical trial ICF. In control arm were 92 patients matched for same conditions as experimental arm patients (matched for location, age, stage, gender, ECOG PS, fatigue, anemia, and chemotherapy line). Cognitive impairment was detected using cognitive tests HVLT-R, TMT, and COWA after the informed consent form (ICF) has been signed. Following the approval of sponsors and conductors of clinical trials, for the usage of the trial data, the patients in both arms were evaluated.

The Hopkins Verbal Learning Test-revised (HVLT-R) is a brief verbal memory and learning test. The test consists a list of a 12-item words,drawn from three semantic categories, presented in three learning trials, followed by 20-25 delayed free recall, and recognition trials. Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index. We used 2 alternate forms (1 and 2) translated into Croatian for THE purpose of this research.
The COWA test is used as a measure of verbal fluency and executive skills such as working memory, planning and strategy. The task is to generate as many words as possible in 60 seconds for each letter. The raw score was sum of produced words for all letters. For THE purpose of this research we used letters K,P , and S which are proposed as most suitable for Croatian speakers.
The Trial Making Test is a test of visual search, attention, motor function, mental flexibility, and executive function. It consists of two parts, one includes numbers only and the rest combines numbers and letters. The raw score was the number of seconds required to correctly complete the task.

Results:
Median age was 63.5 years, 39% were female, and 11% had poor ECOG PS (=2). Patients had advanced solid tumors (Lung: 32%; colorectal: 27%; breast: 15%; other solid tumors: 26%).
THE average time of follow up and chemotherapy were 14.5 and 6.7 months, respectively. Patients were well balanced between arm in age, gender, overall survival (8.7 months), performance status, locations of tumors, stage, anemia, number of chemotherapy lines, and fatigue (FACIT-F test result).
There were less cognitive impairment in term of chemobrain (detected with HVLT-R, TMT, and COWA tests) in experimental arm than in control arm 21.9% and 39.1% of patients, respectively ($p<0.05$).
Furthermore, patients in control arm had trend to be more anemic (21.9% vs 31.5%) but not statistically significant ($p=0.07$). Data are shown in table 1.

Table 1. Baseline Patient Characteristics and Results

	Patients included in clinical trials	Patients not included in clinical trials	P
N	32	92	
Age median (years)	62.4	63.0	
Male	19 (59.4%)	57 (61.9%)	0.636
ECOS PS 0-1	28 (87.5%)	82 (89.1%)	0.249
Anemic	7 (21.9%)	29 (31.5%)	0.070
Locations of primary cancer			0.073
Colorectal	8 (25.0%)	25 (27.2%)	
Breast	3 (9.4%)	15 16.3%)	
Lung	17 (53.1%)	23 (25.0%)	
Other sites	4 (12.5)	29 (31.5%)	
Religious - yes	21 (65.7%)	64 (69.6%)	
Fatigue (FACIT-F score)	36.8	33.55	NA
Median OS (months)	8.9	8.7	
Chemobrain positive detected with HVLT-R, TMT, and COWA tests	7 (21.9%)	36 (39.1)	p<0.05

NA – not available

Conclusion:
The above trial, to our knowledge, is the first evaluation of chemobrain in patients inside and outside of clinical trials.
Cognitive impairment could significantly influence the willingness of participation in clinical trials independently of clinical trial eligibility criteria.
This data provides more light on importance of psycho-oncological estimation of patients affected by cancer.

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