CRITICAL ANALYSIS OF RANDOMIZED TRIALS ON ELECTROMAGNETIC HYPERTHERMIA: DOUBTFUL EFFECT AND MULTIPLE BIASES

Sergey Roussakow, PhD
Galenic Research Institute for Non-Specific Pathology, Moscow

Tab. 1 RCT on superficial hyperthermia published after 1990

Tab. 2 RCT on deep hyperthermia published after 1990

INTRODUCTION

Hyperthermia in oncology had been extensively studied since 60th. Despite of more than 13 000 publications, 50 monographs and manuals and more than 1 200 clinical trials, hyperthermia is still not accepted as a regular cancer treatment. The current trial was performed for further explanation of this situation.

METHODS

All the available randomized controlled trials (RCT) on hyperthermia (HT) in oncology published after 1990 were studied: 7 RCTs on superficial HT (Tab. 1), 6 RCTs on deep loco-regional HT (Tab. 2) and 1 RCT on whole-body HT (altogether 14 RCTs). All the RCTs were studied from the position of "null hypothesis", i.e. considering HT not effective and/or not safe. These were analysed for 1) efficacy by clinical outcomes, 2) toxicity, 3) biases.

RESULTS AND DISCUSSION

8 of the 14 RCTs were recognized as negative by their authors (Tab. 3). HT significantly improved survival in 2 RCTs only. In other trials, HT didn't effect survival significantly, sometimes worsening it. Improvement of local control was the only significant and permanent effect of those positive RCTs. Careful analysis of all the positive RCTs revealed significant biases (Tab. 4) which affected their results.

Inadequate comparator was the most common bias. Typically this was a low-dose radiotherapy (RT) (Overgaard, 1996; van der Zee, 2000; Harima, 2001). As a result, clinical effect in HT-groups of the trials was worse than in other trials, where adequate RT doses (without HT) was used. Toxicity and expensiveness of thermoradiotherapy (TRT) were higher than of RT alone. Therefore, results of HT RCTs received with inadequate comparator were clinically insignificant. At the same time, HT worsened clinical outcomes when applied vs. adequate control (standard high-dose RT). At least in one case HT with adequate RT control significantly reduced overall survival (Vasanthan, 2005) (Fig. 4). Comparative analysis allows to hypothesise, that improvement of local control in the trials with inadequate comparator was achieved for account of significant decrease of overall survival in comparison with trials with adequate treatment (Fig. 3). Significance of RT dose was clearly demonstrated in the RCT of Overgaard et al. (1996) (Fig. 1): increase of RT dose for 10% led to 120% increase of 2-year local control rate, though effect of HT was 2 times less (60% only).

In Jones et al. (2005) trial, defect of randomization was revealed. As a result, RT dose in HT group was 10% higher than in the control RT group (55 Gy vs. 50 Gy). This difference can explain the received clinical effect in full. Additionally, pre-selection of thermosensitive patients was applied in this trial, though the conclusions of the trial were not limited to thermosensitive patients only. Clinical effect in Harima et al. (2001) trial also could be explained by pre-selection of aged patients (median age in HT group of previously untreated patients was 65 years, though the expected age of the first diagnosis is 55 years) and inadequate RT dose to tumor mass (60.6Gy). It's well known that local control after HT is much better among aged patients (Fig. 2).

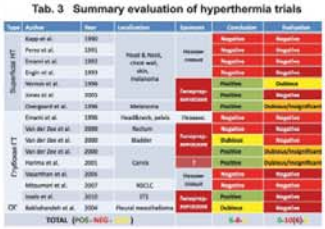
Some trials were incorrectly designed. In Vernon et al. (1996) trial, some different trials were combined in order to reach statistical significance level. Overgaard et al. (1996) trial was experimentally designed. In van der Zee et al. (2000) trial, different protocols were used which are impossible to average. Incomplete data presentation and inadequate analysis are typical biases.

In Issels et al. (2010) trial, systematic distortion in favor of HT group was revealed. As a result, intensity of base therapy in control group was twice lower than in HT group. This distortion excessively explains the received clinical effect without necessity of HT hypothesis. Also, the best results in HT group were much worse than those reported in meta-analysis of 14 earlier RCTs (without HT). This allows to hypothesise that HT possibly worsened the clinical results instead of improve them. This hypothesis is supported by the rise of toxicity in HT group. General toxicity rose 9 times and severe toxicity (treatment-limiting) rose 20 times vs. toxicity in the control group.

The only existing RCT on whole-body HT showed that HT significantly and strongly worsened clinical results comparatively with chemotherapy alone (Fig. 5).

All the RCTs considered as positive by their authors were sponsored by different hyperthermic societies. All the RCTs sponsored by independent organizations were negative.

Tab. 3 Summary evaluation of hyperthermia trials



Tab. 4 Evaluation of biasses in positive RCT

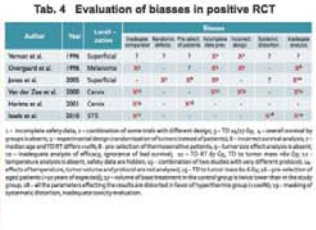
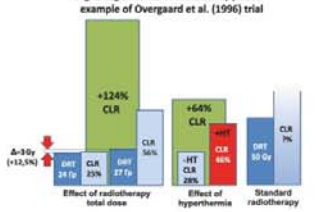
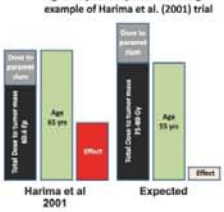


Fig. 1 Significance of radiotherapy dose - example of Overgaard et al. (1996) trial



2 year complete local remission rate (CLR) in the group with total dose (TD) 27Gy was 56% vs. 25% at TD=24Gy (+124%, p<0.05). Therefore, impact of TD for CLR was twice stronger that hyperthermia impact (CLR=46% in hyperthermia group vs. 28% in the control group, +64%). Obviously, with standard TD of DRT (50Gy) the effect of thermal potentiation would be statistically insignificant.

Fig. 2 Impact of special trial design - example of Harima et al. (2001) trial



- **Inadequate control** (TD to tumor mass 60.6 Gy vs. 75-80 Gy with adequate radiotherapy) allows to show effect of thermal potentiation
- **Relatively high dose to parametria** (21.6 Gy or ~25% TD) makes impression of adequate TD (82.2 Gy), reduces relapses rate and makes better survival
- **Pre-selection of aged patients** (+10 years vs. expected age of 1st diagnosis) makes local control better.

Fig. 3 Comparison of RCT on cervix cancer

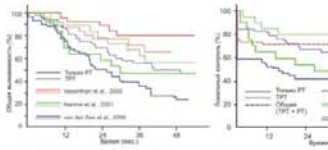


Fig. 4 Decrease of survival in HT group (Vasanthan, 2005)

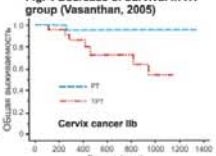
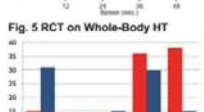


Fig. 5 RCT on Whole-Body HT



In RCT of Bakhshandeh et al. (2004), whole-body hyperthermia (WBH) did worsen effect of chemotherapy (CHT) in malignant pleural mesothelioma. Partial remission (PR) rate in thermo-chemotherapy group (TCHT) was decreased to 18% vs. 31% in control group (CHT only) together with significant decrease of overall survival (OS) (11.5 months vs. 15 months in control group) and disease-free survival (DFS) (5.6 months vs. 9.2 months) and increase of III-IV grade toxicity (neutropenia (NP) 36% vs. 30% in control group, thrombocytopenia (TP) 38% vs. 19% in control group).

Bakhshandeh A, Wiedemann G, Zabel P, et al. Randomized trial with ICE (fosfamide, carboplatin, etoposide) plus whole body hyperthermia versus ICE chemotherapy for malignant pleural mesothelioma. //Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post Meeting Edition). Vol. 22, No. 14S (July 15 Supplement), 2004: 7288.

ABSTRACT

Hyperthermia in cancer treatment still remains an experimental treatment without real clinical future. For further explanation of this situation, all the available randomized clinical trials (RCT) on electromagnetic hyperthermia (EMHT) were studied from the position of 'null hypothesis', taking into account the probable biases. The careful analysis hasn't confirmed a clinical efficacy of EMHT despite of its type: superficial, deep (locoregional) or whole-body. There is no any positive trial not affected with serious biases. After adjustment to the biases, there is no any trial with significant effect of EMHT. EMHT efficacy was shown either in trials with experimental design or versus incorrect comparator. In clinical setting and with correct comparator, EMHT was ineffective or not enough effective to counterbalance its obvious limitations – toxicity and labor-intensity. Since EMHT doesn't generally improve the results obtained with standard effective treatment protocols but significantly increases toxicity, its usefulness is doubtful in general, because an equal or even better effect could be obtained by applying a standard high-dose protocols of radiotherapy or chemotherapy, with lower toxicity and significantly lower labor costs.

Publication: 1. Reported on XXX annual ICHS meeting (Tbilisi, 9-11 сентября 2011 г.)
2. Submitted to «Medical Radiology and Radiation Safety» Journal