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ANTI-TUMOUR TREATMENT

Comparative survival with diverse chemotherapy regimens for cancer of unknown primary site: Multiple-treatments meta-analysis

Vassilis Golfinopoulos [a], George Pentheroudakis [b], Georgia Salanti [c], Andreas D. Nearchou [d], John P.A. Ioannidis [c,e], Nicholas Pavlidis [b,*]

[a] Department of Medical Oncology/Digestive Oncology, Jules-Bordet Institute, Brussels, Belgium
[b] Division of Medical Oncology, University of Ioannina, School of Medicine, Ioannina, Greece
[c] Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina, School of Medicine, Ioannina, Greece
[d] Medical Oncology Clinic Sörmland, Mälarsjukhuset, Eskilstuna, Sweden
[e] Department of Medicine, Tufts University School of Medicine, Boston, MA, USA

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SUMMARY

Objectives: To synthesize the evidence from randomized controlled trials concerning systemic treatment regimens for patients with cancer of unknown primary site (CUP).
Data sources: PubMed and the Cochrane Library Central Registry of Controlled Trials.
Review methods: We retrieved all randomized controlled trials comparing at least two arms of different systemic treatment regimens or a systemic regimen to no treatment in patients with CUP, excluding data on favorable subset CUP, whenever these could be separated. Treatments were categorized according to whether they involved platinum, taxane, both, or neither; non-platinum/non-taxane regimens were also categorized in monotherapy and combination regimens. We extracted or estimated the logarithm of the hazard ratio and its variance for death for each randomized comparison. Multiple-treatments meta-analysis with a hierarchical Bayesian model obtained summary hazard ratios with 95% credibility intervals.
Results: Ten articles were eligible for the meta-analysis. No trials compared systemic treatment to best supportive care and all arms referred to chemotherapy regimens. Overall 683 subjects were randomly assigned and eight randomized comparisons were used for the multiple-treatments meta-analysis of survival (543 patients). Multiple-treatments meta-analysis showed no significant benefit for any treatment group over others, with wide credibility intervals. Point estimates of hazard ratios favored platinum, taxane, or both (hazard ratios 0.69, 0.66, and 0.81, respectively, as compared with monotherapy with an agent other than platinum or taxane).
Conclusion: No type of chemotherapy has been solidly proven to prolong survival in patients with CUP. Regimens using either platinum or taxanes or both need further testing.

Introduction

Cancer of unknown primary site (CUP) is a troubling clinical condition for the practicing oncologist and the cancer patient. It represents 2–5% of all cancers diagnosed.[1,2] About 15–20% of the patients develop CUP that closely resembles one of the major known tumor types (e.g., breast or ovarian adenocarcinoma, head and neck squamous-cell carcinoma, germ-cell tumors) (favorable subsets) and can be successfully treated along the relevant guidelines.[3,4] For the rest (unfavorable subsets), treatment decisions are mostly arbitrary and prognosis is poor. By definition, CUP is metastatic at diagnosis; therefore, except palliative local measures, treatment needs to be administered systemically.

Chemotherapy regimens have been evaluated for CUP in single-arm and randomized trials. Although no clear-cut recommendation can be made for specific drugs in this setting, current European Society for Medical Oncology (ESMO) guidelines suggest platinum-based chemotherapy as the optimal choice.[5] Taxane–platinum combinations are also frequently used in patients with CUP, as they form a regimen with activity in various tumor types.[3,6] This combination has been tested in at least five phase II studies.[7–11]

There is, however, no clear understanding of the survival benefits provided by different regimens, if any. We performed a meta-analysis of randomized controlled trials comparing different chemotherapy regimens in CUP patients that could not be categorized in a favorable subset. As relevant trials have experimented

* Corresponding author. Address: Division of Medical Oncology, University of Ioannina School of Medicine, Niarchou Avenue, 45500 Ioannina, Greece. Tel.: +30 2651099394.
E-mail address: npavlid@uoi.gr (N. Pavlidis).

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with a diverse range of regimens, we used multiple-treatments meta-analysis (MTM) methodology.[12] This allowed us to integrate data from both direct and indirect comparisons in probing the strength of the evidence.

Methods

Search strategy and eligibility criteria

We aimed to present the available evidence from randomized controlled trials concerning systemic treatment regimens for patients with CUP. We searched PubMed and the Central Registry of Controlled Trials of the Cochrane Library. The search string used was '(cancer OR carcinom* OR neoplas* OR malignan*) AND ("unknown primary" OR "occult primary" OR "primary metastatic") AND (random* OR "controlled trial" OR "clinical trial" OR "randomized controlled trial" OR placebo OR "double-blind")'. The last search update was performed on March 27, 2009. We also perused the references of retrieved articles. We cross-searched PubMed using the names of the lead authors in eligible trials.

We considered all randomized controlled trials published as original articles in any language comparing at least two arms of different systemic treatment regimens (different agents or schedules) or a systemic regimen to no systemic treatment (best supportive care), in patients with CUP. Trials were included regardless of line of treatment. We excluded non-randomized trials and pseudo-randomized trials; data on CUP of a favorable subset, unless favorable-prognosis patients could not be separated from the study population; data on known-primary cancer or non-epithelial cancer; trials comparing radiotherapy, hormonal and gene therapy (unless the above regimens were the same in all compared arms and the difference pertained to the chemotherapeutic regimens only); and arms comparing local routes of administration (e.g., intra-arterial). In cases of overlap or duplicate reports, we retained the data with the longest follow-up.

Data extraction

From each eligible trial we recorded the first author, publication year, journal, sample size (randomized and considered eligible for survival analyses, total and per arm), regimens compared, line of treatment, and the percentage of patients with performance status 2 or worse (Karnofsky score 70 or worse) per arm. The type of treatment regimen was categorized according to whether it involved platinum (either cisplatin or carboplatin), a taxane (either paclitaxel or docetaxel), both, or neither a platinum or a taxane in a monotherapy or a combination. We grouped all other regimens together and excluded them from the meta-analysis categorization.

For each trial, we recorded the median survival and the number of deaths per arm, if available, and whether there was a statistically significant difference in survival between the compared arms (two-tailed $P < 0.05$). For trials with more than two arms, we assessed statistical significance for each pair of comparisons separately. For trials that compared at least two different types of chemotherapy regimens, we also extracted or estimated the logarithm of the hazard ratio (log[HR]) and its variance for death. We used the reported hazard ratios (HR) and 95% confidence intervals (CI) from Cox regressions. We preferred unadjusted hazard ratios to multivariate ones. When data on HRs and their uncertainty for survival were not available, we requested this information from the trial investigators; when information was still unavailable, we imputed HRs and their variance using the number of events (E_1, E_2) and randomized patients (T_1, T_2) in each arm and the presented log-rank P value. We estimated the variance of the log(HR) by the formula $(T_1 + T_2)^2/[(E_1 + E_2)T_1T_2]$ and then the natural logarithm of the hazard ratio using the P value denoted by the log-rank test. When P values were not available, we approximated HRs by the ratio of the median survivals.

Data were extracted by three investigators (AN, VG, and JPAI). We discussed discrepancies to reach consensus.

Statistical analyses

We generated descriptive statistics for trial and study population characteristics across eligible trials. Death was the endpoint of interest. We conducted a series of direct meta-analyses summarizing the log-hazard ratios assuming a random effects model. We estimated between-study heterogeneity using the I^2 statistic. These estimates should be interpreted cautiously, as they can have large uncertainty in the presence of few trials.[13,14]

Multiple-treatments meta-analysis is a method of synthesizing information from a network of trials. For details, we refer to the supplement and previous methodological descriptions.[15,12,16–18] We performed multiple-treatments meta-analysis with a hierarchical Bayesian model. We present effect sizes along with 95% credibility intervals. We also estimated the posterior probability that each treatment is the best and the 95% CrI for the relative rank of each treatment based on the adopted Bayesian framework. Analyses were conducted in WinBUGS, version 1.4 (MRC Biostatistics Unit, Cambridge, UK, http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml).

Disclaimers

No sponsors were involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. All authors had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

The search yielded 332 items, 283 from PubMed and 49 from the Cochrane Central Register of Controlled Trials. Of those, upon further detailed screening, we found 10 articles reporting on eligible clinical trials.

The 10 trials[19–28] were published from 1980 to January 2009 (Table 1). We found no trials that compared systemic treatment to best supportive care. All treatment arms referred to chemotherapy regimens. Four trials[23,26,27] stated that they excluded at least some good prognosis subsets. For the rest of the trials, exclusion of favorable subset patients was not stated in the eligibility criteria; however, almost all acknowledged in the introduction the worse prognosis of unfavorable subsets. No trial focused on patients of a favorable subset. In eight reports no previous chemotherapy was allowed for metastatic disease; the other two did not mention the line of treatment.[19,25] Median sample size was 73 (interquartile range 49–87 patients). Overall, 683 subjects were randomly assigned across 20 arms. There was considerable variability in the percentage of patients with poor performance status (median 24.5%, interquartile range 12.8–38.9%), with no clear change over time.

Sixteen different regimens were tested in the 10 trials. Only one monotherapy (5-fluorouracil) and two combinations of different agents (doxorubicin plus mitomycin-C and cisplatin plus doxorubicin plus mitomycin-C) had been tested in at least two trial arms each. The most commonly used drug, platinum compounds (cisplatin or carboplatin), had been used in nine arms. Fluorouracil (with or without leucovorin) had been used in five arms, mitomy-