Original Study

Hypomethylating Agents-associated Infections—Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Data regarding the effects of hypomethylating agents on the risk of infections are lacking. Therefore, we conducted a systematic review and meta-analysis of all randomized controlled trials comparing hypomethylating agent-containing regimens with any other regimen for patients with myeloid neoplasms. Treatment with hypomethylating agents was associated with an increase in the grade 3/4 infection rate compared with the comparator.

Background: The reported data regarding the effects of hypomethylating agents (HMAs) on the risk of infections seem to be poorly documented and heterogeneous. We conducted a systematic review and meta-analysis of all randomized controlled trials comparing HMA-containing regimens with any other regimen administered to patients with myeloid neoplasms. **Materials and Methods:** A comprehensive search was conducted until February 2018. Two reviewers appraised the quality of the trials and the extracted data. The primary outcome was grade 3/4 infections. The secondary outcomes included febrile neutropenia, fever of unknown origin, grade 3/4 neutropenia, infection-related mortality, and all-cause mortality. The relative risks (RRs) and 95% confidence intervals (CIs) were estimated and pooled. A fixed-effect model was used to pool the data unless significant heterogeneity was present, in which case a random-effects model was used. **Results:** We identified 9 trials reported from 2002 to 2016 and randomizing 2184 patients. HMAs were associated with an increase in grade 3/4 infections compared with the comparator (RR, 1.30; 95% CI, 1.02-1.66). This was true for the subgroup of patients aged >60 years (RR, 1.19; 95% CI, 1.01-1.39). In addition, HMAs resulted in an increase in the rate of fever of unknown origin and neutropenia (RR, 1.48; 95% CI, 1.15-1.92; RR, 1.48; 95% CI, 1.22-1.78, respectively). Although no difference was found in the incidence of fatal infections (RR, 1.44; 95% CI, 0.72 to 2.89), treatment with HMA reduced the incidence of all-cause mortality (RR, 0.74; 95% CI, 0.66-0.88). **Conclusion:** Treatment with HMAs was associated with an increase in the grade 3/4 infection rate.

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Introduction

The hypomethylating agents (HMAs), 5-aza-2′-deoxycytidine (decitabine) and 5-azacitidine (azacitidine) are pyrimidine analogues, that target aberrant DNA methylation and restore the expression of tumor suppressor genes by inhibiting DNA methyltransferase.[1] At present, HMAs are considered the standard of care for elderly patients with high-risk myelodysplastic syndrome (MDS) who are not candidates for allogeneic stem cell transplantation[2] and an emerging treatment option for those with acute myeloid leukemia (AML).[3,4] Treatment with HMAs has demonstrated a survival benefit for patients with high-risk MDS and a borderline survival

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benefit for patients with AML.[4] Although HMAs are considered to be safe and are usually administered within an outpatient setting, infectious complications remain a main concern.[5-7] Data regarding the effects of HMAs on the risk of infection seem poorly documented and heterogeneous.

Although early pivotal randomized controlled trials (RCTs) of HMAs demonstrated a low risk of infection,[2,8] later retrospective studies reported a more substantial infection rate. For example, in a retrospective study of 173 patients, Merkel et al[9] showed that 54% of high-risk MDS and AML patients treated with azacitidine developed infectious events. A significant proportion of these patients required hospitalization. In addition, the death rate was 16%.[9] More recently, Schuck et al[10] described a similar infectious rate, with 71% of high-risk MDS patients treated with azacitidine developing infectious complications, 6% of which culminated in death. Several risk factors for infections in patients treated with HMAs have been reported in retrospective studies, including early treatment cycles, poor cytogenetics, a high revised International Prognostic Scoring System (R-IPSS) score, previous intensive chemotherapy, higher HMA dose, and peripheral blood cytopenias.[9,11-14]

We conducted a systematic review and meta-analysis to assess the risk of infectious episodes in patients with high-risk MDS and AML treated with HMAs.

Materials and Methods

Meta-analyses are exempt from institutional or national ethical committee approval, because they do not include individual participants.

Data Sources

The following data sources were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) reported in the Cochrane Library (issue 12, December 2017), PubMed (1966 to December 2017), and conference proceedings of the American Society of Hematology (2005-2017), the American Society of Clinical Oncology (2005-2017), and the European Hematology Association (2005-2017), and the databases of ongoing and unpublished trials (available at: http://www.controlled-trials.com/; http://www.clinicaltrials.gov/ct; and http://clinicaltrials.nci.nih.gov/).

We cross-searched the terms: hypomethylating, azacitidine, and decitabine. The results were limited to RCTs using a highly sensitive filter.[15] We scanned the references of all included trials and reviews identified to find additional studies.

Study Selection

Eligible studies included all RCTs assessing adult patients aged >18 years with a morphologically proven diagnosis of AML or MDS. According to the current World Health Organization classification system, AML is defined as the presence of > 20% blasts in the marrow or blood.[16] Previously, using the French-American-British (FAB) classification system, patients with 20% to 29% blasts in the blood or marrow were classified in the MDS subgroup of refractory anemia with an excess of blasts in transformation.[17] We thus also included earlier studies in which MDS was defined as ≤ 30% of blasts.

We included trials comparing HMA-containing regimens (alone or combined with other chemotherapeutic agents) with any other regimens. We included both patients receiving an HMA as first-line therapy and patients receiving an HMA as maintenance therapy. Trials were included regardless of publication status, date of publication, and language. For cases in which several reports were available for the same study, the most relevant data were included. Two of (L.S., A.G.) conducted the search and applied the inclusion criteria independently.

Data Extraction and Quality Assessment

Two of us (L.S., A.G.) independently extracted the data from the included trials. In the event of a disagreement between the 2 reviewers, a third reviewer (R.G.) extracted the data, and the results were attained by consensus. Both reviewers (L.S., A.G.) independently assessed the risk of bias in the included trials using the Cochrane Collaboration's tool for assessing the risk of bias. We individually assessed the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data reporting, and selective outcome reporting. We separately assessed each domain and graded it as a low risk of bias, unclear risk, or high risk of bias according to the criteria specified in the Cochrane Handbook, version 5.1.0.[15]

Definition of Outcomes

The primary outcome measure was grade 3/4 infection as defined in the individual trials. When the definition in the trials was unclear, we defined grade 3/4 infection using the Common Terminology Criteria for Adverse Events, version 4.03, as an infection treated with intravenous antibiotic, antiviral, or antifungal agents or a life-threatening infection associated with septic shock, hypotension, or acidosis.[18] The secondary outcomes included febrile neutropenia, fever of unknown origin (FUO), grade 3/4 neutropenia, infection-related mortality, and all-cause mortality. In addition, data regarding other infections such as bronchitis, pneumonia, cellulitis, and herpes simplex were collected.

Data Synthesis and Analysis

Dichotomous data were analyzed by calculating the risk ratio (RR) for each trial with 95% confidence intervals (CI) (Review Manager [RevMan], version 5.2, for Windows, The Cochrane Collaboration, Oxford, UK).

We assessed the heterogeneity of the trial results using a χ^2 test to calculate the heterogeneity and the I^2 measure for inconsistency. We used a fixed-effects model with the Mantel-Haenszel method to pool the trial results throughout the review,[19] unless statistically significant heterogeneity was found ($P < .10$ or $I^2 > 50\%$), in which case, we used a random-effects model and the DerSimonian and Laird method.[20] The comparisons were subcategorized by the type of drug. The subgroup analyses for grade 3/4 infection were planned for MDS patients and patients aged ≥ 60 years.

Results

The search yielded 516 potentially relevant titles, 31 of which were considered for further investigation. Of these, 23 trials were excluded for various reasons (Figure 1). We found 9 trials in 11 publications conducted from 1994 to 2014 and reported from 2002 to 2016, randomizing 2184 patients, that fulfilled the inclusion criteria.