Review Article
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Management of Refractory/Relapsed Acute Leukemia with Heart Limitation by Anthracycline-free Chemotherapy Regimens in Pediatric Patients: New Hypothesis and New Approach

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Abstract

Background: Anthracycline therapy for acute leukemia may be associated with significant morbidity and mortality in children or elderly patients that have a degree of heart failure. Patients with prior anthracycline exposure, those with pre-existing heart disease, or who have received the total anthracycline dose present an increased risk for cardiotoxicity. Therefore, new chemotherapy regimens in these situations would be life saving for leukemia patients. We have conducted a systematic review of possible strategies for rescue regimens without anthracycline in refractory acute leukemia patients.

Methods: We gathered the data from 5 creation databases and relevant website until August 2016. We selected randomized clinical trials or other studies that used anthracycline-free chemotherapy regimens to treat acute refractory leukemia in children and adults. The quality of the studies was evaluated according to the Cochrane risk of the polarization tool. All stages of the review were independently conducted by two authors. We obtained data from 75 main clinical trials.

Results: There were 75 trials included from which 4 were considered to be at low risk for bias. Most trials showed that the improvement did not reach statistical significance.

Conclusion: Evidence existed to support the use of the combination of fludarabine, cytarabine, and filgrastim, ICE-rituximab chemotherapy regimens, or monoclonal antibodies such as tyrosine kinase inhibitors (Sorafenib) useful for acute refractory/relapsed leukemia.These drugs are used as first salvage regimens or clofarabine and cladribine for acute myeloid leukemia in patients for whom combined anthracycline chemotherapy is inappropriate.

Keywords: Acute leukemia, Non-antracycline regimen, Cardiac toxicity, Chemotherapy

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Introduction

Anthracyclines are one of the most effective compounds in chemotherapy. The adverse effect attributed to these drugs is cardiotoxicity that develops into heart failure.[1] With the aim to maintain the cumulative dose in the normal range, miscellaneous prevention processes can be achieved by the pediatric oncologist to decrease the risk of cardiotoxicity. Regular cardiac monitoring and administration of dexrazoxane and/or the use of a liposomal doxorubicin preparation are effective methods prior to the full cumulative dose.[2]

The selection of an effective, new chemotherapy regimen poses a challenge in acute leukemia patients that relapse following a full cumulative dose of anthracyclines or in patients with antracycline induced heart failure. Therefore, it is necessary and challenging to find a successional strategy instead of anthracyclines.

Establishing a balance between a prescribed suboptimal chemotherapy dosage by the oncologist and preventing relapse of acute leukemia is a challenge. Several methods have been used to reduce cardiotoxicity of the initial exposure to anthracyclines to protect myocardial function.[3]

Pediatric oncologists may administer another chemotherapy regimen to leukemia patients with heart disease, which is similar to elderly patients. This appears to be a valuable outcome in pediatric oncology, but this hypothesis should be explored in a sufficient number of clinical trials.

In adults, new regimens administered based on clofarabine,vosaroxin, sorafenib, fludarabine, and cladribine may effectively replace anthracycline-based regimens in pediatric patients that have refractory/relapsed (R/R) leukemia.

Materials and Methods

Search methods

We obtained data from Pubmed, Medline, Embase, Google Scholar, and CINAHL from August 1995 until August 2016, in addition to a search of relevant websites. English language papers were included and we collected expert opinions or information from seminars such as the American Society of Hematology annual meetings, oral presentations, and abstract papers.

Selection criteria

This review included data from free antracycline chemotherapy regimens for acute refractory leukemia that used a controlled study design (with or without randomization). We included studies that evaluated interventions, policies or programs in place for 12 weeks or more.

Inclusion criteria for selected articles consisted of: publication date between 1995 and 2016; article in English peer-reviewed journals; study was done to minimize bias; identification of all relevant studies; and sufficient similarities between the selected studies to make combining them reasonable.

Exclusion criteria consisted of: not published as a full article (conference proceedings excluded); published in a language other than English; the studied population had underlying disorders except for cancer; and systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals, editorials, commentaries, letters, news articles, case reports, or narrative reviews.

Two review authors independently extracted data and assessed the risk of bias for the included studies.

Main results

Clinical questions of this review included the following question. What chemotherapy regimens are appropriate for refractory relapsed acute leukemia patients with antracycline induced cardiac toxicity?

The research team developed a study protocol to address research questions for the pediatric patient population with acute leukemia. The review included additional studies and related studies found for this update based on the following key words:

"Refractory relapsed acute leukemia AND antracycline free chemotherapy regimens" (10/50),

where the first number was the number of located articles. The second was the number of related articles. Next, we found a number of drugs for recurrent refractory acute leukemia that were the basis for chemotherapy-free anthracycline regimens, such as: vosaroxin, cytarabine, fludarabine, clofarabine, cladribine, sorafenib, and the ICE protocol.

"refractory relapsed acute leukemia vosaroxin plus cytarabine" (3/12)

"refractory relapsed acute leukemia AND cytarabine " (30/95)

"refractory relapsed acute leukemia AND fludarabine " (34/66)

"refractory relapsed acute leukemia AND clofarabine " (25/56)

"refractory relapsed acute leukemia AND cladribine " (33/45)

"refractory relapsed acute leukemia AND ICE protocol " (2/10)

"refractory relapsed acute leukemia AND sorafenib " (24/45)

All studies were screened for children aged 0-18 years or weak elderly adult patients. Review articles included 19 studies of "acute leukemia AND anthracycline free chemotherapy regimens" in children and antracycline free chemotherapy regimens, although the observed heterogeneity rate was high (I2=82%).

We observed heterogeneity in both age groups (adult and pediatric) that could not be explained by the status of randomization or the type, duration, or extent of the intervention.

We found strong evidence that supported the beneficial effects of some chemotherapy drugs which could replace anthracyclines such as rescue or salvage plans in acute leukemia in adults. However, because of unexplained heterogeneity and probability of a low bias study, these results should be interpreted with caution. A wide range of program components were used in these studies, although it was impossible to distinguish which of these components had the most contribution to the observed beneficial effects. Our synthesis indicated the following promising policies and strategies. In the final review we selected 13 articles. Their main results are presented in the references.

Results

We included a total of 75 trials; 4 were considered to be at low risk for bias. Most trials showed that the improvement did not reach statistical significance.

Sorafenib-based regimen

Sorafenib tosylate is a synthetic compound that targets growth signaling and angiogenesis. It affects the critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation. Sorafenib blocks the enzyme RAF kinase. In addition, sorafenib inhibits the VEGFR-2/PDGFR-beta signaling cascade and, as a result, blocks tumor angiogenesis. Sorafenib with low-dose cytarabine in patients with heart failure is used for R/R acute leukemia.[4-7]

Sorafenib, as a FLT3-ITD inhibitor drug, is an effective treatment in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) with the FLT3-ITD mutation . Patients should receive subcutaneous administration of cytarabine (10 mg/m^2 bid) on days 1-10 and oral sorafenib tosylate at doses of 200-600 mg/1.73 m^2 bid on days 2-28. Sorafenib tosylate is added to salvage chemotherapy regimens as a targeted therapy. The anti-leukemic effects of sorafenib and azacytidine have been evaluated in FLT3-ITD + cell lines *in vitro*. Sorafenib and azacitidine showed synergistic inhibition of cell proliferation and apoptosis induction. Subsequently, consolidation azacitidine (100 mg/day × 4 days) subcutaneously every four weeks until disease progression or allogeneic Hematopoetic stem cell transplantation was administered. The total dose of 400 mg per cycle was similar to that used for the maintenance of AML. A 4-day decision-making scheme was practical to avoid wasting medicines and to shorten the duration of administration.[8-11]

Vosaroxin-based regimens

Vosaroxin, is a quinolone-derived intercalating

agent. Initial clinical studies have shown that it is well-tolerated in weak patients with R/R acute leukemia. A synergistic effect with cytarabine (Ara-C) must be considered. Vosaroxin is administered at 90 mg/m^2 intravenously on days 1 and 4 in the first cycle, followed by 70 mg/m^2 in subsequent cycles, and cytarabine (1 g/m^2, intravenously on days 1-5).

Vosaroxina has shown reliable results when combined with cytarabine and might be of clinical benefit to some patients with R/R AML. In elderly patients with acute R/R AML, the situation is similar to pediatric patients with heart failure.[12-20]

Clofarabine-based regimen

Clofarabine is a second generation purine nucleoside analog designed to overcome the limitations and incorporate the best qualities of cladribine and fludarabine. Clofarabine enters the cells by passive transport through lipid membranes, as well as the transport of active nucleosides. Unlike cladribine, clofarabine is active in both AML and ALL. Although cladribine was not active in adult leukemia and induced neurotoxicity in this population, clofarabine showed activity in adult leukemia and did not induce the neurotoxicity associated with other nucleoside analogs. One patient with AML who received clofarabine monotherapy remained in complete remission for 43 weeks without therapy. Once inside the cell, clofarabine is phosphorylated to its active triphosphate form by cellular kinases, including deoxycytidine kinase. While fludarabine and cladribine only inhibit ribonucleotide reductase and DNA polymerase, respectively, clofarabine inhibits both enzymes.[22-24]

In some regimens, the efficacy and safety of administration of intravenous clofarabine (40 mg/m^2), cyclophosphamide (440 mg/m^2), and etoposide (100 mg/m^2) for 5 consecutive days in R/R pediatric patients showed encouraging response rates and sustained remission in R/R patients.[25-28]

In addition, daily intravenous clofarabine (20 mg/m^2) administration for 5 days and cytarabine (20 mg subcutaneously) twice daily for 10 days is an effective regimen. Clofarabine with low dose of alternate cytarabine and decitabine in consolidation phase is effective in newly diagnosed AML patients with heart conditions.

It seems these regimens are an appropriate approach for first treatment in refractory AML in patients who cannot receive anthracycline. The benefits of prolonged consolidation remain unproven. Additional randomized controlled trials are needed to directly compare the efficacy of clofarabine as a single agent and in combination therapy compared with intensive chemotherapy regimens.[30-34]

Fludarabin-based regimen

Fludarabine phosphate is 2-fluoro, a 5'-monophosphate derivative of vidarabine (Ara-A) with improved solubility. The mechanism of cytotoxic action of the compound appears to involve the metabolic conversion of the active triphosphate.[35,36]

Fludarabine has a substantial activity against lymphoid malignancies. The most popular regimen against lymphoid malignancies is the FLAG protocol that includes two fludarabine 30 mg/m^2/day + Ara-C 2 g/m^2/day for days 1-5 and G-CSF (5 mcg/kg/day) from day 0 to recovery of polymorphonuclear cells. Elderly patients with untreated AML are administered FLAG as initial induction chemotherapy at some adult centers. Primary induction with FLAG in elderly AML patients achieves a high remission rate without prohibitive mucosal or cardiac toxicity and may be considered as an alternative to standard anthracycline-based regimens in this setting.

The FLAG regimen is a non-anthracycline based regimen that may serve as an alternative to the standard induction regimens for AML in older adults or those with significant co-morbidities that include preexisting cardiac disease. It is associated with comparable remission rates and acceptable overall survival in older patients. In addition, it may allow some patients with preexisting cardiac disease to proceed to allo-SCT.[43-47]

ICE-rituximab regimen

Rituximab (375 mg/m^2) was administered on days 1 and 3 of each cycle, ifosfamide (3000 mg/m^2) and etoposide (100 mg/m^2) administered on days 3, 4 and 5, and carboplatin (635 mg/m^2) administered only on day 3.[48-50] ICE-rituximab is administered for 1 to 3 cycles depending on the response.

The combination of rituximab and ICE chemotherapy have safe, acceptable toxicity. At the end of the protocol, some patients could possibly proceed to consolidation with high dose therapy and stem cell rescue. This chemotherapeutic regimen, without the use of an anthracycline drug, has an outcome comparable to other regimens for adult acute leukemia. These regimens were well-tolerated by several ranges patients with acute leukemia, including pediatric patients. The ICE protocol combined with rituximab in childhood Burkitt's leukemia in patients with poor prognoses is useful.[51]

Cladribine (2-CdA)-based regimen

Cladribine (2-CdA) is an adenosine deaminase resistant analog of adenosine induce apoptosis of myeloid cells. 2-CdA has activity in R/R myeloid neoplasms such as pediatric AML with a complete response (CR) rate of 47%. Several studies have confirmed the efficacy of single agent 2-CdA or 2-CdA combination regimens in AML. Established CR rates for combination regimens in R/R adults were approximately 50%, while CR rates for ND adults were approximately 70% and showed similar toxicity profiles to previously used regimens. Despite these promising data, many centers have yet to adopt 2-CdA combination regimens for these difficult-to-treat populations.[52-55]

Cladribine with cytarabine (Ara-C) and G-CSF (CLAG regimen), and re-induction therapy were administered in patients with R/R AML. The protocol consisted of 2-CdA (5 mg/m^2 for 2 hours of infusion per day) for 5 consecutive days. A 4-hour infusion of Ara-C (2 g/m^2) for 2 hours was administered after each 2-CdA infusion. G-CSF (300 microgram) was administered 24 hours prior to the first dose of 2-CdA for 6 days.

In patients with CR, the consolidation treatment begins with a treatment that contains 2-CdA.[56-60] The CLAG regimen has shown significant anti-leukemia activity and acceptable toxicity as reinduction treatment in R/R AML patients. This regimen, CLAG-M, is a well-tolerated, highly effective salvage regimen in poor risk R/R AML. In primary refractory disease, CR was 45.5% for CLAG.[61-63]

Conclusion

Development of an experimental regimen in R/R pediatric acute leukemia remains a clinical challenge, especially without anthracyclines. Evidence exists to support the use of FLAG chemotherapy. ICE-rituximab regimens or monoclonal antibodies such as tyrosine kinase inhibitors (Sorafenib) or clofarabine, cladribine are non-anthracycline agents useful for acute R/R leukemia as a first salvage treatment among AML patients that cannot use anthracyclines..

In the absence of a common therapeutic approach, physicians should compare all currently available methods, including chemotherapy-free anthracycline regimens, targeted therapy, and allogeneic HSCT, or a combination of these as a life-saving options for R/R acute leukemia.

Conflict of Interest

No conflict of interest is declared.

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