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Review article

Therapeutic options for leukemic transformation in patients with myeloproliferative neoplasms

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ABSTRACT

Approximately 5–10% of patients with Philadelphia chromosome negative myeloproliferative neoplasms (MPN) comprising of essential thrombocythemia, polycythemia vera and primary myelofibrosis) experience transformation to acute myeloid leukemia (AML, ≥20% blasts). Treatment options for post-MPN AML patients are limited, as conventional approaches like standard chemotherapy, fail to offer long-term benefit. Median survival for secondary AML is ~2.4 months. Post-MPN AML therefore represents an area of urgent clinical need. At present, allogeneic stem cell transplant (ASCT) following induction therapy is the best therapeutic option. Patients ineligible for ASCT are treated with hypomethylating agents. New agents under investigation include histone deacetylase inhibitors, JAKinhibitors and agents targeting the BRD4 protein. Combined treatment strategies involving these novel agents are being tested. In this review we present the current evidence regarding treatment options for post-MPN AML patients.

1. Introduction

The Philadelphia-negative myeloproliferative neoplasms (MPNs) are a group of clonal hematopoietic stem cell disorders that are phenotypically related to each other. They comprise of polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).

Transformation to acute myeloid leukemia (AML) (or MPN-blast phase [BP]) [1], is characterized by ≥20% blasts in bone marrow or peripheral blood according to the World Health Organization [2], and is one of the most feared complications of MPN. Approximately 5–10% of all MPNs progress to AML within 10 years of diagnosis [3]; this includes 1% of cases of ET, 4% of cases of PV, and 20% of cases of PMF [4]. Among 605 patients with ET, Mayo Clinic investigators reported leukemic transformation (LT) in only 20 cases (3.3%) at a median follow-up of 84 months [5]. Owing to limited data and difficulty in performing large-scale clinical trials, there is limited understanding of this progression.

Although risk factors for LT have not been fully established, advanced age (> 60 years) and exposure to chemotherapy are known to increase risk of transformation. The molecular basis of this progression is also not well understood and remains an area of current research. Therapy-related leukemia most often exhibits *AML1* mutations [6], but may also possess other cytogenetic abnormalities such as *TP53*, *MLL*, and *EVI-1* gene mutations [7]. In a study of 417 MPN patients evaluated between 1985 and 2007 (152 having PV, 212 having ET, 29 having PMF, and 24 having unclassified MPN), a total of 18 (4.3%) progressed to leukemia within a minimum follow-up duration of 12 months. Five of these 18 patients were found to have *AML1/RUNX1* mutations at LT, however these mutations were not present in the chronic phase of MPN. The results of this study indicated that *AML1/RUNX1* point mutations may indeed have leukemogenic potential and may promote LT in MPN [8].

A somatic mutation implicated in the pathogenesis MPN is JAK2 V617F. It is a gain-of-function mutation and has been a major target of treatment strategies in recent years [9,10]. This particular mutation has been identified in > 90% of patients with PV and 50% of those with MF and ET, and is mostly absent in patients with *de novo* AML. This divergent biology of post-MPN AML may explain the failure of standard AML therapies, including induction chemotherapy, to improve outcomes in post-MPN AML [11,12]. Genetic studies of paired samples of patients with MPN describe at least two different mechanisms of leukemic transformation. A subset of patients with JAK2-positive MPN progressed to JAK2-positive AML; this was associated with the acquisition of additional genetic alterations [13–16]. The other, more complex path to AML involves JAK2-positive MPN followed by JAK2-

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negative AML [17,18]. This advanced understanding of the molecular mechanisms and genetic alterations leading to this transformation is providing rational targets for novel innovative treatment.

In addition to biological risk factors such as abnormal karyotype and leukocytosis [19], treatment with cytoreductive agents has also been implicated in the transformation process. These agents include oral alkylating agents such as melphalan [20] and pipobroman [21,22]; radioactive phosphorus [23–25]; and splenectomy [26]. Risk associated with use of hydroxyurea remains a subject of controversy, with a number of studies giving conflicting results [3,27–38]. Some studies have found higher rates of LT in patients treated with hydroxyurea, but this may be attributable to the fact that biologically aggressive MPNs that require therapy, are also more likely to transform, rather than that the treatment itself induces LT.

A case of an unclassified myelodysplastic syndrome/MPN with acute LT has also been reported in a patient with ovarian cancer after exposure to paclitaxel and carboplatin-based chemotherapy [39]. Moreover, an independently increased risk of MPN-BP has been suggested in patients exposed to erythroid-stimulating agents and androgens, particularly danazol [40].

Patients with LT have median overall survival duration of only 2.6 months [11,19]. Standard induction chemotherapy has been shown to extend overall survival duration to 3.9–5 months [41]. Overall survival in these patients is limited by a high relapse rate and significant treatment-related mortality [12]. A retrospective analysis of 273 post-MPN AML patients diagnosed between 1989 and 2016 concluded no difference in outcome by MPN subtype or by treatment type (hypomethylating agents, high-dose cytarabine, low-dose cytarabine and 'other'). No improvement in survival outcomes was observed from 1989 to date [42].

This review aims to analyze the available data regarding treatment of LT in patients with MPN and to highlight newer strategies.

2. Supportive therapy and low-dose chemotherapy

In a study carried out among leukemic patients at Princess Margaret Cancer Center between January 1998 and July 2011 [12], Kennedy et al. found that 75 patients had a dual diagnosis of MPN and AML (73 patients met the formal definition of LT, and 2 others developed myeloid sarcoma after MPN). These patients were broadly divided into those treated with curative intent (38 patients), and those treated with non-curative intent (37 patients); the latter received supportive therapy and non-intensive chemotherapy. Patients who participated in a clinical trial and those treated with one chemotherapeutic agent were considered to have received non-intensive chemotherapy (16 patients). Those given only standard medical care, transfusions, and cytoreduction with hydroxyurea (without other chemotherapeutic agents) were considered to have received supportive therapy (21 patients). Reasons for receiving either supportive therapy or non-intensive chemotherapy included the following: age > 70 years (26 patients), poor performance status (2 patients), significant medical comorbidities (3 patients), personal choice (4 patients) and lack of a donor for allogeneic stem cell transplantation (ASCT; 1 patient, who had achieved complete remission). The most commonly used chemotherapeutic agents were azacitidine, decitabine, and low-dose cytarabine. Among the 16 patients who received non-intensive chemotherapy, the majority did not show a favorable response: only 2 patients reverted to the chronic MPN phase or achieved complete remission. One patient subsequently developed AML following unclassified MPN and was given azacitidine. The patient had stable disease with a consistent drop in blast count until he died of infection, 15 months after the diagnosis of AML. The second patient developed FAB-M6 AML after ET and was treated with combination decitabine and vorinostat. Complete remission was achieved after 8 cycles of treatment, but the patient was not a candidate for ASCT owing to his age. Compared to the entire cohort, the group of patients treated with non-curative intent had significantly poorer survival outcomes, with a 2-year overall survival rate of 3.1% and a median overall survival duration of 2.3 months.

In another study [11], Mesa et al. found that 91 of 2333 patients diagnosed with MF with myeloid metaplasia fulfilled the World Health Organization criteria for LT [2]. They were divided into three treatment categories: AML-like induction chemotherapy (24 patients), low-intensity chemotherapy where the target was palliation (19 patients), and supportive care (48 patients). Survival was defined as the interval from the date of diagnosis of LT to either death or last contact. Low-intensity chemotherapy included weekly vincristine (2 mg/m^2 per week), oral alkylators, low-dose subcutaneous cytarabine and oral etoposide among other agents. Induction chemotherapy consisted of continuous infusion cytarabine (5–7 days) plus anthracycline (2–3 days); high-dose cytarabine (> 1000 mg/m^2 per dose); mitoxantrone in combination with VP-16 plus high-dose cytarabine; or gemtuzumab. Supportive therapy included antibiotics, platelet or erythrocyte transfusions, and oral chemotherapy with hydroxyurea for prevention of leukostasis. The median overall survival duration in this group was just 2.0 months (range 0.0–20.1 months). None of these regimens produced a sustained effective response (median overall survival for the whole cohort was 2.9 months; range 0.4–22.5 months).

Both these studies therefore concluded that supportive therapy and low-dose chemotherapy were unable to improve prognosis.

Effective targeted chemotherapeutic agents that are currently available include two hypomethylating agents that have been approved by the US FDA for MPN and post-MPN LT. These are 5-aza-2′deoxycitidine (decitabine) and 5-azacytidine (azacitidine). Both of these agents incorporate into DNA; azacitidine additionally incorporates into RNA. They form a covalent complex with the enzyme DNA methyltransferase, trapping and degrading the enzyme, resulting in subsequent DNA hypomethylation. At very high doses, the cytotoxic effects of the agents predominate. However, lower doses are postulated to allow hypomethylation and therefore, epigenetic modulation [43]. These agents are discussed individually below.

2.1. Decitabine

Decitabine is an S-phase specific agent activated by deoxycytidine kinase. Once activated by the enzyme, decitabine makes a pyrimidine analogue that integrates into DNA, causing irreversible inhibition of DNA methyltransferase. This hypomethylating agent has been used in MF to alleviate splenomegaly and anemia [44,45].

Hypermethylation of p15/p16 gene promoter sites has been reported in patients with MF-BP but not in chronic-phase MF [46]. Additionally, studies in NOD/SCID mouse models have shown that in vitro treatment of PMF CD34+ cells with hypomethylating agents followed by histone deacetylase inhibitor can result in preferential redirection of abnormal stem cells back to the bone marrow. This occurs through upregulation of CXCR4 in PMF CD34+ cells [47,48]. Another phase II study of low-dose decitabine demonstrated a 37% response rate in MF, including in two patients with MF-BP [45]. All of these studies, therefore, support the use of decitabine in patients with MPN-BP.

In a retrospective study carried out by Mascarenhas et al. [49], eleven patients with MF-BP were treated with decitabine and/or ASCT. Four patients received ASCT only. Patients who required treatment prior to ASCT or were ineligible for ASCT were given decitabine. Five patients with MF-BP received decitabine alone, 1 patient received decitabine for MF-BP after developing LT following myeloablative ASCT, and 1 patient received decitabine prior to ASCT. Patients were treated with decitabine at a rate of 20 mg/m^2 intravenously over 1 h for 5 days (range of 2–10 cycles). Patients received decitabine every 28 days for up to 6 cycles consecutively and were also given packed red blood cell and platelet transfusions to maintain hemoglobin above 8 g/dL and a platelet count above 20,000/μL. Of the six patients who received decitabine, three (50%) died after 5, 7, and 10 months of LT. The remaining three patients were still alive at 8+, 12+, and 45+ months