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Leukemic transformation in myeloproliferative neoplasms: Therapy-related or unrelated?

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Polycythemia vera, essential thrombocythemia, and primary myleofibrosis are chronic myeloproliferative neoplasms (MPNs) associated with an increased morbidity and mortality. MPNs are also associated with progression to acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS). The "true" rate of transformation is not known mainly due to selection bias in clinical trials and underreporting in population-based studies. The outcome after transformation is dismal. The underlying mechanisms of transformation are incompletely understood and in part remain an area of controversy. There is an intrinsic propensity in MPNs to progress to AML/MDS, the magnitude of which is not fully known, supporting a role for nontreatment-related factors. High doses of alkylating agents, P^{32} and combined cytoreductive treatments undoubtedly increase the risk of transformation. The potential leukemogenic role of hydroxyurea has been a matter of debate due to difficulties in performing large prospective randomized trials addressing this issue. The main focus of this review is to elucidate therapy-related leukemic transformation in MPNs with a special focus on the role of hydroxyurea.

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Introduction

Polycythemia vera (PV) and essential thrombocythemia (ET) are chronic myeloproliferative neoplasms (MPNs) with an increased morbidity and mortality mainly caused by thrombohaemorrhage diathesis and a variable progression to myelofibrosis (MF), myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) [1,2]. The third classical Philadelphia chromosome-negative MPN is primary myelofibrosis (PMF) which is complicated by anemia, splenomegaly and transformation to AML/MDS. For many years now there has been a debate whether the evolution to AML/MDS is an inherent characteristic of this group of disorders or associated with the use of cytoreductive drugs to control the overproduction of erythrocytes, platelets and leukocytes [3,4]. Overall there appears to be an agreement on the notion that both intrinsic MPN-related as well as extrinsic treatment-related factors play a role in the transformation of MPNs to AML/MDS. We still need to improve methods to identify individuals carrying an increased risk of acquiring this most often fatal complication. As described in further detail below, the use of high doses of alkylating agents and radioactive phosphorous (P^{32})/X-ray treatment is consistently associated with an increased risk of leukemic transformation. In addition, interferon-α and anagrelide are to a very high degree of certainty non-leukemogenic. A clearly controversial issue is whether the antimetabolite hydroxyurea adds to the intrinsic propensity of MPNs to transform to AML/MDS [3–5]. Several factors contribute to this lack of knowledge. MPNs remain a small and heterogeneous group of disorders, patients have a long-term clinical course, and transformation is a relatively rare event often appearing several years after diagnosis. These factors together with the reluctance/difficulties to perform well-designed prospective comparative trials have hampered the proper settling of this issue. Since the MPNs have different biological and clinical features, and thereby are exposed to different treatment strategies, PV, ET, and PMF will be discussed separately.

Polycythemia vera

Clinical aspects of AML/MDS progression

PV is the largest group of MPNs constituting approximately half of newly diagnosed patients with a MPN [6]. The overall incidence of progression to AML/MDS in various series ranges between 5% and 15% 10 years after diagnosis and seems to increase with time thereafter [4]. The potential transformation of PV to AML was suggested as early as 1905 when Blumenthal (1905) described a PV patient developing excessive white blood cell counts [7]. Several similar reports were to follow (for references see Ref. [8]). With the introduction of radiation treatment (X-ray or P^{32}) and the increasing number of PV patients reported to have progressed to AML the question arose whether the risk of transformation increased as a result of treatment. This issue was complicated by the argument (not established) that radiation treated patients survived longer than non-exposed PV patients and thus had a greater risk to transform "spontaneously" to AML/MDS. Based on findings from a large retrospective study of 1222 patients with polycythemia (including at least 476 with PV) Modan and Lilienfeld (1965) observed that "11% of the P^{32} and 8.9% of the X-ray treated PV patients developed acute leukemia compared to less than 1% in the non-radiation treated group" [8]. After adjustments for several factors they concluded that "the increased risk of leukemia does not necessarily follow a prolonged survival". Since then the leukemogenic potential of P^{32} has been established also in randomized clinical trials performed by the Polycythemia Vera Study Group (PVSG), and the French Polycythemia Study Group (FPSG) reporting an incidence of 5–15% after an observation period of 10 years [9–11]. In the seminal study by the PVSG (01), 431 PV patients were randomized to one of the following three treatments: phlebotomy alone, P^{32} and phlebotomy, or chlorambucil and phlebotomy [10]. There was an excess number of AML cases in both the P^{32} (9.6%) and chlorambucil (13%) treatment arms. In the phlebotomy only group the incidence of AML was 1.5%, which thus should represent the spontaneous rate of leukemic transformation in PV. However, this low figure seems to be misleading since patients requiring cytoreductive therapy were censored and the number of patients managed by phlebotomy was reduced over time leading to significantly reduced follow-up time [4,12]. In a second randomized trial in patients >65 years of age the FPSG reported 12% acute leukemias at 10 years in patients receiving P^{32} alone. Hydroxyurea