Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

## Vorgang: 2013-B-128 – Ruxolitinib

Stand: Januar 2014

# I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

**Ruxolitinib**
**zur Behandlung chronisch myeloproliferativer Erkrankungen**

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
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| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | *Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.* |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | • Allogene Stammzelltransplantation (für ausgewählte Patienten)<br>• Substitution von Blutprodukten<br>• Splenektomie<br>• Milzbestrahlung |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | • Beschluss vom 7. März 2013 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ruxolitinib: Geringer Zusatznutzen (Erstbewertung als Arzneimittel zur Behandlung eines seltenen Leidens (Orphan Drug) unterhalb der 50-Millionen-Umsatzgrenze). |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | *Siehe systematische Literaturrecherche.* |
| Bei mehreren Alternativen ist die wirtschaftlichere Therapie zu wählen, vorzugsweise eine Therapie, für die ein Festbetrag gilt. | *Entfällt.* |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Beratungsanforderung/Fachinformation) |
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| Zu prüfendes Arzneimittel: | |
| Ruxolitinib<br>L01XE18<br>(Jakavi®) | Zugelassenes Anwendungsgebiet:<br>Jakavi® ist angezeigt für die Behandlung von krankheitsbedingter Splenomegalie oder Symptomen bei Erwachsenen mit primärer Myelofibrose (auch bekannt als chronische idiopatische Myelofibrose), Post-Polycythaemia-vera-Myelofibrose oder Post-Essentieller-Thrombozythämie-Myelofibrose. (FI Jakavi® 10-2013) |
| **Im Bereich des Anwendungsgebietes zugelassene Arzneimittel:** | |
| Hydroxycarbamid<br>L01XX05<br>(Litalir®, Syrea®) | Behandlung von Patienten mit essentieller Thrombozythämie oder Polycythämia vera mit hohem Risiko für thromboembolische Komplikationen.<br>(FI Syrea® 11-2013) |
| Anagrelid<br>L01XX35<br>(Xagrid®) | Xagrid® ist zur Verringerung der erhöhten Thrombozytenzahl bei Risikopatienten mit essentieller Thrombozythämie [= > 60 Jahre und/oder Thrombozytenzahl > 1.000.000 /µl und/oder thrombohämorrhagische Ereignisse in der Anamnese] vorgesehen, die ihre derzeitige Therapie nicht vertragen oder deren erhöhte Thrombozytenzahl durch ihre derzeitige Therapie nicht auf ein akzeptables Maß gesenkt werden kann.<br>(FI Xagrid® 05-2013) |

Quellen: AMIS-Datenbank, Lauer-Taxe, Leitlinien, EMA

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# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie:

## Inhalt



## Indikation für die Recherche bei Wirkstoff (evtl. Markenname):

Jakavi® (Ruxolitinib) ist angezeigt für die Behandlung von krankheitsbedingter Splenomegalie oder Symptomen bei Erwachsenen mit primärer Myelofibrose (auch bekannt als chronische idiopatische Myelofibrose), Post-Polycythemia-vera-Myelofibrose oder Post-Essentieller-Thrombozythämie-Myelo-fibrose.

## Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel: s. Unterlage zur Beratung in der Arbeitsgruppe Übersicht zweckmäßige Vergleichstherapie, Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“.

## Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „Myelofibrose, Splenomegalie, Polycythemia Vera, Thrombocythemie “ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 22.01.2014 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, NGC, TRIP, DAHTA, NIHR HSC. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, DGHO-Onkopedia, NCCN, *NCI, ESMO.* Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und

europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 253 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 49 Quellen eingeschlossen. Die Evidenzsynopse enthält ergänzend eine Darstellung pivotaler Studien von besonderer Bedeutung. Insgesamt ergab dies *17* Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

**IQWIG Berichte/ G-BA Beschlüsse**

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| **G-BA, 2013:** Beschluss<br><br>des Gemeinsamen Bundesausschusses<br><br>über eine Änderung der Arzneimittel -Richtlinie<br><br>(AM-RL): Anlage XII - Beschlüsse über die<br><br>Nutzenbewertung von Arzneimitteln mit neuen<br><br>Wirkstoffen nach § 35a SGB V – Ruxolitinib [16] | Jakavi® ist angezeigt für die Behandlung von krankheitsbedingter Splenomegalie oder Symptomen bei Erwachsenen mit primärer Myelofibrose (auch bekannt als chronische idiopathische Myelofibrose), Post-Polycythaemia-vera-Myelofibrose oder Post-Essentieller-Thrombozythämie-Myelofibrose.<br><br>Ruxolitinib ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 gilt der medizinische Zusatznutzen durch die Zulassung als belegt.<br><br><u>Vergleich</u>: Ruxolitinib vs. Kontrolle (Placebo bzw. BAT)<br><br><u>Ausmaß des Zusatznutzens:</u><br><br>Geringer Zusatznutzen. |

**Cochrane Reviews**

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| **Squizzato et al. (2008):** Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. [14] | 1. Fragestellung: To quantify the benefit and harmof antiplatelet drugs for long-termprimary and secondary prophylaxis of arterial and venous thrombotic events in patients with polycythaemia vera or essential thrombocythaemia. |
| | 2. Methodik:<br>Population: Patienten mit einer Polycythaemia vera oder einer essentiellen Thrombozythämie<br><br>Intervention: Thrombozytenaggregationshemmer (Aspirin, Ticlopidin, Clopidogrel, Dipyridamol)<br><br>Komparator: Placebo oder Nichtbehandlung<br><br>Endpunkt:<br>• Primäre Endpunkte: Mortalität durch arterielle und venöse thrombozytische Störungen, tödliche Blutungen<br>• Sekundäre Endpunkte: Jedes tödliche oder nicht-tödliche arterielle und venöse thrombozytische Störung, jedes Mikrozirkulations-Ereignis, jede flüchtige neurologische und okulare Manifestation, schwere und nicht-schwere Blutungen, Gesamtmortalität, allgemeine unerwünschte Ereignisse.<br><br>Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche bis 2007.<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 RCTs mit N= 630 Patienten |
| | 3. Ergebnisdarstellung<br>• **Allgemein:** Keine ausreichenden Daten für eine time-to-event Datenanalyse, für sowohl den definierten primären als den sekundären Endpunkten. Daher beruht die durchgeführte Metaanalyse auf vier Hauptendpunkten (einzelne binäre Endpunkte).<br>• Numerische, jedoch nicht stat. signifikante, Vorteile unter einer Therapie mit Aspirin gegenüber Placebo hinsichtlich des Risikos eine tödliche thrombozytische Störung zu erleiden (OR: 0.20; 95%KI: 0.03-1.14 / 19/1000 tödliche thrombozytische Störungen können unter Aspiringabe verhindert werden; 95%KI: 0-40). Gleichzeitig erhöhte eine Aspiringabe nicht das Risiko auf ein schweres Blutungsereignis (OR: 0.99; 95%KI: 0.23-4.36).<br><br>*Hinweis: Diese Studien beziehen sich nur auf Patienten mit einer Polycythaemia Vera, es wurden keine Studien zu Patienten mit einer essentiellen Thrombozythämie identifiziert.* |
| | 4. Fazit der Autoren: The available evidence suggests that the use of aspirin is associated with a statistically non-significant reduction in the risk of fatal thrombotic events, without an increased risk of major bleeding, when compared with no treatment in patients with polycythaemia vera who have no clear indication or contraindication to aspirin therapy.<br><br>5. Anmerkungen:<br>• Allgemein eingeschränkte Analysemöglichkeiten durch:<br>o Wenig Studien<br>o Studien nur zu einem Krankheitsbild |

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| **Squizzato et al. (2013):** Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia [15]<br><br>*<u>Hinweis</u>: Update des CC aus dem Jahr 2008!* | 1. Fragestellung: To quantify the benefit and harm of antiplatelet drugs for long-term primary and secondary prophylaxis of arterial and venous thrombotic events in patients with polycythaemia vera or essential thrombocythaemia. |
| | 2. Methodik<br>Population: Adult (age ≥18 years) participants with polycythaemia vera or essential thrombocythaemia, diagnosed by established international criteria (e.g.World Health Organization (WHO), Polycythaemia Vera Study Group (PVSG)).<br><br>Intervention: Antiplatelet drug (e.g. aspirin, ticlopidine, clopidogrel, dipyridamole, prasugrel, ticagrelor)<br><br>Komparator: Placebo or no treatment for at least 6 months.<br><br>Endpunkt:<br>• <u>Primäre Endpunkte:</u> Mortalität durch arterielle und venöse thrombozytische Störungen, tödliche Blutungen<br>• <u>Sekundäre Endpunkte:</u> Jedes tödliche oder nicht-tödliche arterielle und venöse thrombozytische Störung, jedes Mikrozirkulations-Ereignis, jede flüchtige neurologische und okulare Manifestation, schwere und nicht-schwere Blutungen, Gesamtmortalität, allgemeine unerwünschte Ereignisse.<br><br>Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche bis 2012.<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 RCTs mit N= 630 Patienten. Es wurden keine neuen Studien identifiziert. |
| | 3. Ergebnisdarstellung<br><u>*Note*</u>: Only two RCTs were finally included in this systematic review (GISP 1997; ECLAP 2004). Both studies included only participants with polycythaemia vera, and in both trials, the administered antiplatelet drug was aspirin given at low dose. We did not find and therefore did not include any new studies in our update search. An ongoing study, which was potentially eligible, was identified from a search of the online trial registry.<br><br><u>Ergebnisse wie in **Squizzato et al. 2008:**</u><br>• Published data from both studies were insufficient for a time-to-event data analysis and for some of the primary and secondary outcomes that we planned.<br>• The use of low-dose aspirin, compared with placebo, was associated with a lower risk of fatal thrombotic events (although this benefit was not statistically significant (OR 0.20, 95% CI 0.03 to 1.14; P = 0.07).<br>• No data on mortality from bleeding episodes were available. A non-significant benefit of aspirin was shown for all-cause mortality (OR 0.46, 95% CI 0.21 to 1.01; P = 0.05).<br>• No increase in the risk of major bleeding was reported in participants taking aspirin compared with those given placebo (OR 0.99, 95% CI 0.23 to 4.36; P = 0.99), and a non-significant increase with aspirin treatment was shown for minor bleeding (OR 1.85, 95% CI 0.90 to 3.79; P = 0.09).<br>• No published studies have reported findings in participants with essential thrombocythaemia or in the study of other antiplatelet drugs. |

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| | 4. Fazit der Autoren<br>*For patients with polycythaemia vera who have no clear indication or contraindication to aspirin therapy, available evidence suggests that the use of low-dose aspirin, when compared with no treatment, is associated with a statistically non-significant reduction in the risk of fatal thrombotic events and all-cause mortality, without an increased risk of major bleeding.*<br><br>5. Anmerkungen: siehe **Squizzato et al. 2008** |

**Systematische Reviews**

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| **Gu et al. 2013:** Ruxolitinib for myelofibrosis [5] | 1. Fragestellung: To assess the beneficial and harmful effects of ruxolitinibin patients with myelofi brosis (MF). |
| | 2. Methodik:<br>Population: Patients with myelofi brosis (MF) (patients with intermediate risk, high risk or not determined MF, including PMF, post-PV MF and post-ET MF)<br><br>Intervention: Ruxolitinib<br><br>Komparator: Placebo or the best available therapy<br><br>Endpunkt:<br>• Primäre Endpunkte: The primary outcome measures were: i) the proportion of patients that had a reduction in spleen volume of ≥35% at 24 weeks; ii) the proportion of patients that had a reduction in spleen volume of ≥35% at 48 weeks.<br>• Sekundäre Endpunkte: i) overall survival rate; ii) all adverse events, including non-haematological and haematological adverse events, serious adverse events, necessary dose reductions or interruptions and treatment discontinuations.<br><br>Suchzeitraum (Aktualität der Recherche): The Cochrane databases, PubMed and Embase were searched for studies published up to October 2012.<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): Two trials randomised 528 patients. |
| | 3. Ergebnisdarstellung<br>*Note*: The present study aimed to perform analyses on the following subgroups: i) MF type (PMF, post-PV MF or post-ET MF). BUT: Subgroup or sensitivity analyses were not conducted in the present study due to the lack of sufficient trial numbers.<br><br>It was not possible to perform meta-analysis as the two studies included had different comparison interventions and were not groupable.<br>• Compared with the placebo, ruxolitinib had a significant beneficial effect on the proportion of patients that had a reduction in spleen volume of ≥35% at 24 weeks [OR: 109.78; 95% CI: 14.97-804.78] or an increased overall survival rate (OR: 2.02; 95% CI, 0.99-4.12).<br>• Ruxolitinib significantly increased the risk of several non-haematological or haematological adverse events, but not the risk of treatment discontinuations (OR: 1.04; 95% CI, 0.50-2.14).<br>• Compared with the best available therapy (nicht definiert), ruxolitinib had a significant beneficial effect on the proportion of patients that had a reduction in spleen volume of ≥35% at 24 (OR: 68.45; 95% CI, 4.15-1129.19) or 48 weeks (OR: 56.20; 95%CI, 3.40-928.67).<br>• Ruxolitinib significantly increased the risk of several non-haematological adverse events, serious adverse events and dose reductions or interruptions (OR: 9.60; 95% CI, 4.66-19.81), but not the risk of treatment discontinuations (OR: 1.54; 95% CI, 0.48-4.97). |
| | 4. Fazit der Autoren:<br>In conclusion, based on the trials included in the present study, the use |

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| | of ruxolitinib is beneficial in the treatment of MF.<br><br>5. Anmerkungen:<br>• In the two randomised controlled trials on ruxolitinib in MF, the method to generate randomisation sequences was not stated, concealment of randomisation was not mentioned, information on blinding was not available in one study, the total number of included patients was small, follow-up was insuffi cient and no data were obtained on changes in marrow fi brosis or the JAK2V617F allele burden. A potential bias existed due to the limitations of the search strategy in the present study. |

**Leitlinien**

| Empfehlung zur Therapie der Polycythaemia Vera (PV) | |
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| **DGHO (2010):** Polycythaemia Vera (PV) [5] | Fragestellung: Therapieempfehlung zur Indikation der Polycythaemia Vera (PV) |
| | Methodik: Keine Information zum Erstellungsprozess (systematische Suche, Konsensprozess und Literaturbewertung) angegeben. |
| | **A) Kurative Therapie:** Allogene Knochenmark- bzw. periphere Blutstammzellentransplantation<br>Voraussetzung: Ersterkrankungsalter < 35 a, HLA-kompatibler Geschwisterspender<br><br>**B) Palliative/Symptomatische Therapie**<br><br>**Senkung des Thromboembolierisikos:** bestmögliche Einstellung der Blutwerte<br><br>• allgemeine Maßnahmen: Gewichtsnormalisierung, Bewegung, Vermeidung von Exsiccose und langem Sitzen, Reisekompressionsstrümpfe, effektive Behandlung kardiovaskulärer Risikofaktoren, Information über Thrombose-Frühsymptome<br>• **Aderlass** (/Erythrozytapherese)<br>• **ASS** (Thrombozytenaggregationshemmung – grundsätzlich: alle Patienten & alle Stadien)<br><br>**Bei zunehmend progredienter Erkrankung/Thromboembolierisiko/ Symptomatik:**<br><br>• Zytoreduktive Therapie:<br>o Standardtherapie: **Hydroxycarbamid** (= Hydroxyurea)<br>o bei Versagen/Unverträglichkeit: **Anagrelid** / (**Jak2-Inhibitoren** - in Studien) für alle Altersgruppen<br>< 40 a auch: (Peg)Interferon $\alpha$, > 75 a auch: Busulfan / $P^{32}$ / (Pipobroman)<br><br>**Einzelfälle mit Splenomegalie-bedingten Problemen im späten Krankheitsstadium:**<br><br>• **Milzbestrahlung**, **Splenektomie** (hohes Morbiditäts- und Mortalitätsrisiko) |
| **European LeukemiaNet: Philadelphia-Negative Classical Myeloproliferative Neoplasms (2011):** Critical Concepts and Management Recommendations [2] | Fragestellung: Therapieempfehlungen zur Indikation der Polycythaemia Vera (PV) |
| | Methodik: Keine Information zum Erstellungsprozess (systematische Suche, Konsensprozess und Literaturbewertung) angegeben. |
| | **Goal of therapy:**<br>• avoid first occurrence and/or recurrence of thrombotic and bleeding complications<br>• minimize the risk of acute leukemia and post-PV myelofibrosis<br>• control systemic symptoms, treat complications (thrombosis, hemorrhage)<br>• manage risk situations (eg pregnancy, surgery)<br><br>**All patients**<br>• aggressive management for cardiovascular risk factors, smoking cessation<br>• phlebotomy to maintain the hematocrit at less than 45%<br>and |

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| | • low-dose **Aspirin** (until/unless major bleeding, intolerable side effects, allergy, intolerance)<br><br>**Cytoreductive therapy**<br>high-risk patients and patients with poor tolerance of phlebotomy or frequent phlebotomy requirement, symptomatic or progressive splenomegaly, severe disease-related symptoms, platelet counts greater than 1500 x $10^9$/L, progressive leukocytosis:<br>• **first-line** at any age: **Hydroxyurea** or **Interferon α** (Hydroxyurea should be used with caution in patients **< 40 a**)<br>**> 70 a**: **Busulfan** may be considered<br>• **second-line**:<br>o Interferon α (nonleukemogenic) or Hydroxyurea<br>o in patients with short life expectancy: Pipobroman, Busulfan, P. |
| **National Cancer Institute (2011):** Polycythemia Vera [1] | Fragestellung: Therapieempfehlungen zur Indikation der Polycythemia Vera |
| | Methodik*:*<br><br>The PDQ editorial boards use a formal ranking system of levels of evidence to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. For any given therapy, results can be ranked on each of the following two scales: (1) strength of the study design and (2) strength of the endpoints. Together, the two rankings give an idea of the overall level of evidence. Depending on perspective, different expert panels, professional organizations, or individual physicians may use different cut points of overall strength of evidence in formulating therapeutic guidelines or in taking action; however, a formal description of the level of evidence provides a uniform framework for the data, leading to specific recommendations.<br><br>**<u>Ranking system:</u>**<br><br>*1. Randomized controlled clinical trials.*<br>*i. i.Double-blinded.*<br>*ii. ii.Nonblinded treatment delivery.*<br><br>2. *Nonrandomized controlled clinical trials.*<br><br>3. *Case series.*<br>*i. Population-based, consecutive series.*<br>*ii. Consecutive cases (not population-based).*<br>*iii. Nonconsecutive cases.*<br><br>**1. Phlebotomy** (intermittent, chronic phlebotomy)<br>aim: maintain hematocrit in ♂ < 45%, in ♀: maybe lower (e.g. < 40% - no empiric data to confirm this recommendation)<br><br>complications: progressive / extreme thrombocytosis, symptoms of chronic iron deficiency: i.e. pica, angular stomatitis, glossitis.<br><br>[Antihistamines to control pruritus] |

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| | **2. Hydroxyurea** (alone or with phlebotomy)<br>many clinicians use hydroxyurea for patients who require cytoreductive therapy that is caused by massive splenomegaly, a high phlebotomy requirement, or excessive thrombocytosis.<br><br>**3. (pegylated) Interferon α**<br>Pooled analysis of 16 trials: avoidance of phlebotomy in 50% of patients, marked reduction of splenomegaly in 80% of patients, no cases of acute leukemia [Level of evidence: 3iiiDiv]. Problems: cost, side effects, i.v. administration<br><br>⇨ treatment with (peg)interferon is considered for patients < 50 years (more likely to tolerate the side effects and benefit from a lack of transformation to leukemia) who are poorly compliant with phlebotomy or issues of massive splenomegaly, leukocytosis, or thrombocytosis supervene, while hydroxyurea is considered for patients > 50 years.<br><br>**4. Chlorambucil or Busulfan**<br>may rarely be required, especially if Interferon or Hydroxyurea are not tolerated, as is often seen in patients older than 70 years: The PV Study Group randomly assigned more than 400 patients to phlebotomy (target hematocrit < 45), $P^{32}$ (radioisotope phosphorous$^{32}$, 2.7 mg/m$^2$ i.v. every 12 weeks as needed), or Chlorambucil (10 mg/d for 6 weeks, then given daily on alternate months). Median survival for the phlebotomy group (13.9 years [a]) and the $P^{32}$ group (11.8 a) was significantly better than that of the Chlorambucil group (8.9 a), primarily because of excessive late deaths from leukemia or other hematologic malignancies. [Level of evidence: 1iiA]<br><br>**5. Low-dose ASS**<br>≤ 100 mg daily, unless contraindicated by major bleeding or gastric intolerance<br><br>Cochrane review of two randomized studies: reduction of fatal thrombotic events (not statistically significant, OR = 0.20; 95% CI, 0.03-1.14). |
| **Nodric MPD Study Group (2008):** Guidelines for the diagnosis and treatment of patients with polycythemia vera, essential thrombocythemia and primary myelofibrosis. [11] | Fragestellung: Therapieempfehlungen zur Indikation der Essentiellen Thrombozythämie (ET) |
| | Methodik<br><br>The Nordic study group on myeloproliferative disorders (NMPD) is a pan-Nordic organisation that has conducted Nordic clinical trials since 2001. NMPD decided in 2006 to write new guidelines, based on already existing national guidelines from the Nordic countries, Italy and Great Britain. The first version was published in 2007. The aim has been to write a document that can be used in all Nordic countries. We have strived to use evidence-based medicine, i.e the conscientious, explicit, and judicious use of current best evidence in making decisions on our recommendations. However, it should be stressed that few randomized controlled trials exist in the MPDs to support decision-making for individual patients. The guidelines are written for health professionals with a speciality or interest in haematology. They have now been updated in 2008, incorporating the new diagnostic criteria established by the World Health Organization.<br><br>**Grading system:** |

**A) Levels of evidence**

| Level | Type of evidence |
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| Ia | Evidence obtained from meta-analysis of randomised trials |
| Ib | Evidence obtained from at least one randomised controlled trial |
| IIa | Evidence obtained from at least one well-designed controlled study without randomisation |
| IIb | Evidence obtained from at least one other type of well-designed quasi-experimental study |
| III | Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies |
| IV | Evidence obtained from expert committee reports and/or clinical experiences of respected authorities |

**B) Grades of recommendation**

| Grade | Evidence level | Recommendation |
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| A | Ia, Ib | Required: At least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation |
| B | IIa, IIb, III | Required: Availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation |
| C | IV | Required: Evidence obtained from expert committee reports or opinions and /or clinical experiences of respected authorities.<br>Indicates absence of directly applicable studies of good quality |

**Choice of cytoreductive therapy in PV (Recommendations):**

- **HU:**
  - Hydoxyurea is recommended as one first-line cytoreductive therapy in PV **(Grade A recommendation, evidence level Ib).** *Note: HU is not recommended during pregnancy*
  - The concern for leukaemia transformation with long term HU treatment and the recent favourable results of IFN treatment with a reduction in JAK2 allele burden makes IFN the drug of choice in PV, especially in younger patients. The use of HU should therefore be limited in patients below 60 years **(Grade C recommendation, evidence level IV).**
- **Interferon-alpha:**
  - IFN-α is theoretically superior for treating PV as it is effective in controlling proliferation of all cell lineages and there is no risk of leukemogenesis. Molecular remissions can be acheived with IFN. It is most likely to be tolerated in patients below 60 years for whom it is recommended. Pegylated forms of IFN seem equally effective as conventional IFN **(Grade B recommendation, evidence level III).**
  - Since the median time to clinical response to interferon is long, patients with platelet values >1500 or with a vascular complication (demanding prompt lowering of platelet values) should receive hydroxyurea as initial therapy, and later on be switched to interferon.
- **Anagrelide:**
  - Anagrelide may be used to control thrombocytosis in PV patients that cannot tolerate or do not respond to IFN or HU, and when HU is considered a less suitable alternative due to a concern for an increased leukemic risk **(Grade C recommendation, evidence level IV).**
- **Combination therapy**
  - In clinical practice where it is sometimes difficult to reach the desired treatment goal due to side effects of single agents, combination

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| | therapy with HU and anagrelide, IFN and anagrelide, or HU and IFN may have advantages since side effects can be reduced with retained or improved clinical efficacy. However, no studies of such combinations have yet been published.<br>• **Busulfan:**<br>o Low dose ***intermittent*** busulfan is more efficacious in controlling PV than 32P (**Grade A recommendation, evidence level Ib).**<br>o Since busulfan is an alkylating agent it should be reserved for patients 75 years or older, or for patients not tolerating HU, IFN or anagrelide **(Grade B recommendation, evidence level III)**<br>• **Radioactive phosphorus (32P):**<br>o 32P is effective in PV, but less so than *intermittent* busulfan. Since it increases the leukaemic transformation rate its use should be limited to patients older than 75 years **(Grade A recommendation, evidence level Ib)**<br>**Non-recommended therapeutic options in PV**<br>Imatinib, Pipobroman, Chlorambucil**.** |
| **Empfehlung zur Therapie der Essentiellen Thrombozythämie (ET)** | |
| **DGHO (2010):** Essentielle Thrombozythämie (ET) [12] | Fragestellung: Therapieempfehlung zur Indikation der Essentiellen Thrombozythämie (ET) |
| | Methodik: Keine Information zum Erstellungsprozess (systematische Suche, Konsensprozess und Literaturbewertung) angegeben. |
| | **A) Kurative Therapie:** nicht bekannt<br>**B) Palliative/Symptomatische Therapie**<br>• **Senkung des Thromboembolierisikos:** Alle Patienten & Stadien: bestmögliche Einstellung der Blutwerte, allgemeine Maßnahmen (s.o.: PV)<br>o Niedrigrisiko-Patienten: Sorgfältige Überwachung (Nutzen von ASS / zytoreduktiver Therapie nicht durch prospekt. Studien gesichert)<br>o Intermediärrisiko-Patienten: Thrombozytenaggregationshemmung mit **ASS**<br>o Hochrisiko-Patienten: **< 60 a**: **Hydroxycarbamid** (cave: Neoplasierisiko) / **Anagrelid** / (Peg)**Interferon α; > 60 a**: **Hydroxycarbamid** / Zweitlinie: Anagrelid. |
| **European LeukemiaNet Philadelphia-Negative Classical Myeloproliferative Neoplasms (2011):** Critical Concepts and Management Recommendations. [2] | Fragestellung: Therapieempfehlungen zur Indikation der Essentiellen Thrombozythämie (ET) |
| | Methodik: Keine Information zum Erstellungsprozess (systematische Suche, Konsensprozess und Literaturbewertung) angegeben. |
| | **Goal of therapy:**<br>• avoid first occurrence and/or recurrence of thrombotic and bleeding complications (vgl. = PV)<br>• minimize the risk of acute leukemia and post-ET myelofibrosis<br>• control systemic symptoms, treat complications (thrombosis, hemorrhage)<br>• manage risk situations (eg pregnancy, surgery).<br>**All patients**<br>• aggressive management for cardiovascular risk factors, smoking cessation.<br>• low-dose **ASS** if microvascular disturbances are present. |

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| | **Cytoreductive therapy**<br>high-risk patients and patients with a platelet count greater than 1500 x $10^9$/L (risk factor for bleeding):<br>• **first-line**: at any age: **Hydroxyurea** (should be used with caution in patients < 40 a).<br>• **second-line**: **Anagrelid** (or Interferon $\alpha$): nonleukemogenic-patients receiving > 1 cytotoxic agent: higher risk of developing acute myeloid leukemia/myelodysplastic syndrome in patients with short life expectancy: **Pipobroman, Busulfan, P.** |
| **National Cancer Institute (2011):** Essential Thrombocytemia [10] | Fragestellung: Therapieempfehlungen zur Indikation der Essential Thrombocytemia. |
| | Methodik:<br>The PDQ editorial boards use a formal ranking system of levels of evidence to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. For any given therapy, results can be ranked on each of the following two scales: (1) strength of the study design and (2) strength of the endpoints. Together, the two rankings give an idea of the overall level of evidence. Depending on perspective, different expert panels, professional organizations, or individual physicians may use different cut points of overall strength of evidence in formulating therapeutic guidelines or in taking action; however, a formal description of the level of evidence provides a uniform framework for the data, leading to specific recommendations.<br>**Ranking system:**<br>*1. Randomized controlled clinical trials.*<br>*i. Double-blinded.*<br>*ii. Nonblinded treatment delivery.*<br>*2. Nonrandomized controlled clinical trials.*<br>*3. Case series.*<br>*i. Population-based, consecutive series.*<br>*ii. Consecutive cases (not population-based).*<br>*iii. Nonconsecutive cases.*<br>**1. No treatment**, unless complications develop<br>Low-risk-Patients (< 60 a, platelet count < 1500 × $10^9$/L, asymptomatic)<br>Case-controlled observational study (65 low-risk patients (< 60 a, platelet count < 1500 × $10^9$/L, no history of thrombosis / hemorrhage): thrombotic risk (1.91 cases / 100 patient years [py]) and hemorrhagic risk (1.12 cases / 100 py) not increased over the normal controls. Retrospective review (300 low-risk patients (≤ 60 a, no prior thrombotic episodes): benefit for antiplatelet agents in reducing venous thrombosis in JAK2-positive patients and in reducing arterial thrombosis in patients with cardiovascular risk factors.<br>**2. Hydroxyurea**<br>Hydroxyurea (titrated to attain a platelet count < 600,000/$mm^3$, control group: no therapy) was found to be effective in preventing thrombotic episodes (4% vs. 24%) in patients with a high risk of thrombosis. [Level of evidence: 1iiDiv]<br>A retrospective analysis of this trial found that antiplatelet drugs had no significant influence on the outcome.<br>**3. (pegylated) Interferon $\alpha$** |

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| | **4. Anagrelide**<br>Prospective randomized trial (809 patients) compared hydroxyurea + aspirin vs anagrelide + aspirin: platelet-lowering effect equivalent, significantly more thrombotic and hemorrhagic events (HR = 1.57, P = 0.03) and more myelofibrosis (HR = 2.92, P = 0.01) in the anagrelide group. No differences were seen for myelodysplasia or acute leukemia. [Level of evidence: 1iiA] |
| **Empfehlung zur Therapie der Primären Myelofibrose (PMF)** | |
| **DGHO (2010):** Primäre Myelofibrose (PMF) [4] | Fragestellung: Therapieempfehlungen zu der Indikation der Primären Myelofibrose (PMF) |
| | Methodik: Keine Information zum Erstellungsprozess (systematische Suche, Konsensprozess und Literaturbewertung) angegeben. |
| | **A) Kurative Therapie** (Alter max. 70 a):<br>• Allogene Stammzellentransplantation (SZT) (Mortalität bis 20% ⇨ Risikostratifizierung !) im Rahmen von Studien: autologe SZT (fehlender Spender bei jüngeren Patienten)<br>**B) Palliative/Symptomatische Therapie**<br>**Niedrigrisiko-Patienten & Intermediärrisiko-Patienten 1** ohne klinische Probleme: watch & wait / entsprechende Studie<br>• **Intermediärrisiko-Patienten 2 & Hochrisiko-Patienten:**<br>o **1. Kontrolle einer Hyperproliferation**<br>❖ zytoreduktive Therapie:(Effekt auf Lebenserwartung nicht durch prospektive randomisierte Studien gesichert, Standard: Hydroxycarbamid (Beobachtungen: günstige Auswirkungen auf Progression, Anämie & Lebensqualität) Alternativ: Interferon α, Imatinib, bei prominenter Thrombozythämie: Anagrelid<br>o **2. Patienten mit therapiebedürftiger Anämie und/oder Thrombozytopenie**<br>❖ Bluttransfusion<br>*Erläuterungen: Zur Behandlung einer therapiebedürftigen Anämie werden insbesondere bei zusätzlicher Autoimmun-hämolyse (niedriges Haptoglobin und evtl. positiver Coombs-Test) häufig mit Erfolg Kortikosteroide eingesetzt. Dosierung initial 0,5 mg pro kg Körpergewicht über 3 Wochen, dann Reduktion, nur bei Erfolg Dauertherapie mit kleinen Dosen unterhalb der Cushingschwelle. Ca. 1/3 der Patienten sprechen auf diese Therapie an, die meisten allerdings nur vorübergehend.*<br>❖ Corticosteroide (insbesondere bei zusätzlicher Autoimmunhämolyse)<br>*Erläuterungen: In einigen publizierten Arbeiten wird die Wertigkeit der Erythropoetin-Behandlung in Hinblick auf die PMF-bedingte Anämie beschrieben [6]. Bei einer initialen Gabe von 3 x 10.000 I.E. pro Woche kann mit einem Ansprechen bei ca. der Hälfte der Patienten gerechnet werden. Es kann bis zu 3 Monaten dauern, bis ein Ansprechen auftritt. Komplette Remissionen (keine Transfusionsabhängigkeit mehr und normaler Hb-Wert) treten in ca. 20-25 % der Fälle auf. Ein Serumerythropoetin-Spiegel < 125 U/l ist Voraussetzung für ein günstiges Ansprechen auf* |

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| | *Erythropoetin. Mit pegylierten Langzeitpräparaten werden mindestens die gleichen Ansprechraten erzielt. Unter Erythropoietin ist allerdings Vorsicht geboten, da die Splenomegalie hierunter deutlich zunehmen kann.*<br>❖ Erythropoetin (cave: Splenomegalie, leukämische Transformation)<br>*Erläuterungen: In einigen publizierten Arbeiten wird die Wertigkeit der Erythropoetin-Behandlung in Hinblick auf die PMF-bedingte Anämie beschrieben [6]. Bei einer initialen Gabe von 3 x 10.000 I.E. pro Woche kann mit einem Ansprechen bei ca. der Hälfte der Patienten gerechnet werden. Es kann bis zu 3 Monaten dauern, bis ein Ansprechen auftritt. Komplette Remissionen (keine Transfusions-abhängigkeit mehr und normaler Hb-Wert) treten in ca. 20-25 % der Fälle auf. Ein Serumerythropoetin-Spiegel < 125 U/l ist Voraussetzung für ein günstiges Ansprechen auf Erythropoetin. Mit pegylierten Langzeitpräparaten werden mindestens die gleichen Ansprechraten erzielt. Unter Erythropoietin ist allerdings Vorsicht geboten, da die Splenomegalie hierunter deutlich zunehmen kann.*<br>❖ Androgene (Nandrolon, Danazol): bei transfusionspflichtiger Anämie (Einzelfallberichte)<br>*Erläuterungen: Diese Medikamente sind in Einzelfallberichten bei transfusionspflichtiger Anämie eingesetzt worden. Dosierung von Danazol (Gonadotropinhemmer): 2-3-mal 200 mg/Tag. Die Wirksamkeit kann erst nach 2-3 Monaten beurteilt werden. Falls Androgene starke Nebenwirkungen (Anstieg der Leberwerte, Virilisierung bei Frauen) verursachen, müssen sie abgesetzt werden. Ein Ansprechen der Anämie kann in ca. 50 % der behandelten Fälle erwartet werden.*<br>❖ Thalidomid / Lenalidomid / (Pomalidomid) je + Prednisolon<br>*Erläuterungen: In mehreren Phase II Studien hat sich Thalidomid als wirksame Substanz bei Patienten mit einer hämatopoetischen Insuffizienz, insbesondere in Hinblick auf eine Anämie oder Thrombozytopenie erwiesen. Problematisch sind jedoch die hohen Therapieabbruchraten, die bei etwa 50% unter Thalidomid mit einer Dosis zwischen 50 und 400 mg liegen: In zwei Arbeiten konnte ein vergleichbarer Therapieeffekt bei insgesamt besserer Verträglichkeit auch unter niedrig dosierter Thalidomid-Therapie (50 mg/d) gezeigt werden, wobei die Kombination mit Prednisolon in Hinblick auf Verträglichkeit und Ansprechen mit einem Hb-Anstieg > 2 g/dl in 45 % der Fälle die besten Ergebnisse erzielte:*<br>*Mayo-Schema:*<br>*Thalidomid 50 mg/d + Prednisolon 0,5 mg/kg Körpergewicht (Monat 1); Prednisolon 0,2 mg/kg Körpergewicht (Monat 2); Prednisolon 0,125 mg/kg Körpergewicht (Monat 3).*<br>*Etwas bessere Ansprechraten bei ebenfalls verbesserter Verträglichkeit werden mit den Nachfolgesubstanzen Revlimid und Pomalidomid erzielt. Keines der Imide ist bisher für die Behandlung der PMF zugelassen. In Deutschland ist seit 1/2010 eine prospektive Phase II Studie von der Deutschen Studiengruppe Myeloproliferative Neoplasien (MPN-SG) aktiviert mit Pomalidomid für PMF-Patienten mit Anämie und/oder Thrombozytopenie.* |

- **3. Patienten mit Splenomegalie**
  - Splenektomie: Risiko: perioperative Mortalität 7%: Blutungen, Infektionen, Thrombosen, perioperative Morbidität: 30%

    Nutzen: 1 Jahr nach OP palliativer Nutzen bei 76% der Patienten (Allgemeinbefinden ↑, Splenomegalie-Symptome ↓)
    ⇨ strenge Indikation:
    - Hydroxyurea-resistente symptomatische Splenomegalie
    - schwere portale Hypertension
    - progrediente transfusionspflichtige Anämie

    *Erläuterungen: Splenektomie Die meisten Erfahrungen hierzu werden von der Mayo-Klinik berichtet: Die perioperative Mortalitätsrate lag bei 7% (perioperative Blutungen, Infektionen und Thrombosen) und die perioperative Morbidität bei 30 %. Es gab einen signifikanten Zusammenhang zwischen dem Auftreten einer perioperativen Thrombose und einer postoperativen Thrombozytose. Dennoch konnte nach 1 Jahr für 76% der Patienten ein palliativer Nutzen der Splenektomie, d.h. Besserung des Allgemeinbefindens und fehlende Beschwerden durch die große Milz, belegt werden.*
  - Milzbestrahlung (cave: UE Zytopenie / Komplikationsrate einer späteren Splenektomie ↑)

    *Erläuterungen: Eine Alternative zur Splenektomie bei Hydroxyurea-resistenten Patienten stellt die Milzbestrahlung dar. Eine positive Beeinflussung besteht auch bei ausgeprägten Allgemeinsymptomen. Die durchschnittliche Ansprechdauer nach Bestrahlung beträgt 6 Monate. Wiederholte Bestrahlungen sind im Verlauf möglich. Problematisch sind oftmals ausgeprägte, prolongierte Zytopenien im Anschluss an eine Milzbestrahlung. Die optimale Strahlendosis ist individuell zu bestimmen, da kein linearer Zusammenhang zwischen applizierter Strahlendosis und Entwicklung einer Zytopenie besteht. Die Indikationen für eine Splenektomie sind vor Beginn einer Strahlentherapie zu prüfen, da die Komplikationsraten für die Splenektomie nach Strahlentherapie deutlich ansteigen.*
  - JAK2-Inhibitoren (Ruxolitinib) in Studien: Splenomegalie ↓, Krankheitssymptome ↓ - auch JAK2-negative Patienten sprechen an; Nachteil: Verschlechterung bestehender Anämie / Thrombozytopenie

    *Erläuterungen: In jüngster Zeit sind eine Reihe von Phase II Studien mit Jak2-Inhibitoren angelaufen. Die meisten Daten liegen momentan bei der PMF mit dem Jak2-Inhibitor der Firma Incyte vor. Hier zeigt sich, dass mit diesen Substanzen eine deutliche Verkleinerung von Splenomegalien und eine deutliche Verbesserung von Allgemeinsymptomen (Leistungsminderung, Fieber, Nachtschweiß und Appetitlosigkeit, Gewichtsverlust) zu erreichen ist. Interessanterweise sprechen auch Jak2-negative Patienten an. Der Einfluss der Jak2-Inhibitoren auf die Hämatopoese ist allerdings nicht selten negativ, so dass sich eine Verschlechterung einer bestehenden Anämie und Thrombozytopenie einstellen kann.*

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| **European LeukemiaNet Philadelphia-Negative Classical Myeloproliferative Neoplasms (2011):** Critical Concepts and Management Recommendations [2] | Fragestellung: Therapieempfehlungen zur Indikation der Primären Myelofibrose (PMF). |
| | Methodik: Keine Information zum Erstellungsprozess (systematische Suche, Konsensprozess und Literaturbewertung) angegeben. |
| | Main goals of therapy: prolongation of survival and, if possible, also cure, which is currently only achieved by alloSCT if prolongation of survival or cure is not possible, symptom-orientated palliation and quality of life.<br><br>**Anemia** (hemoglobin value less than 10 g/dL)<br>▪ Erythropoiesis-stimulating agents<br>▪ Corticosteroids<br>▪ Androgens (eg testosterone enanthate, oral fluoxymesterone or danazol)<br>▪ Immunomodulators: Thalidomide (in combination with prednisone), Lenalidomide (in the presence of del(5)(q31))<br><br>**Splenomegaly**<br>▪ Hydroxyurea: drug of choice for symptomatic splenomegaly and for controlling symptomatic thrombocytosis and/or leukocytosis<br>▪ Hydroxyurea-refractory disease: i.v. Cladribine, oral Melphalan, oral Busulfan, (Interferon $\alpha$: poorly tolerated and limited efficacy in PMF)<br>▪ Radiotherapy: transient (median duration 3 - 6 months) symptomatic relief of mechanical discomfort from hepatosplenomegaly, associated with a greater than 10% mortality rate from consequences of cytopenia<br>▪ Splenectomy: treatment of drug-refractory symptomatic splenomegaly<br><br>**Nonhepatosplenic extramedullary hematopoiesis** (thoracic vertebral column and other sites)<br>▪ Low-dose radiation therapy<br><br>**Splenectomy**<br>perioperative mortality: 5 - 10%, postsplenectomy complications: ~ 50% of patients<br>⇨ requires good performance status and absence of clinical or laboratory evidence of disseminated intravascular coagulation.<br>⇨ indications: symptomatic portal hypertension (e, variceal bleeding, ascites), drug-refractory marked splenomegaly –painful or associated with severe cachexia, and established RBC transfusion-dependent anemia.<br>Cytoreduction and anticoagulants are recommended prophylactic measures before splenectomy.<br><br>Severe thrombocytopenia is a marker of leukemic transformation, and overall outcome might not be favorably affected by splenectomy.<br><br>**Allogeneic stem-cell transplantation** (alloSCT)<br>Potentially curative, but complicated by relatively **high treatment-related mortality and morbidity**: conventional-intensity conditioning:1-year treatment-related mortality ~ 30%, OS 50%; reduced-intensity conditioning: 5-year median survival ~ 45% & similar incidence of treatment-related and relapse-related death rates. Comparison: 1- and 3-year survival rates of transplantation-eligible patients (high- or intermediate-risk, age < 60 years) who did not undergo transplantation ranged from 71% to 95% and 55% to 77%, respectively.<br><br>⇨ it is reasonable to justify the risk of alloSCT-related complications in patients whose median survival is expected to be less than 5 years:<br>• high-risk patients (median survival ~ 27 months) & intermediate-2-risk patients (median survival ~ 48 months) |

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| | • patients with RBC transfusion need (median survival, approximately 20 months)<br>• patients with unfavorable cytogenetic abnormalities (median survival, approximately 40 months)<br><br>Adverse factors of outcome: RBC transfusion load, marked splenomegaly, non-HLA-identical sibling donor, not fully HLA-matched donor, increased alloSCT-specific comorbidity index, advanced age, advanced stage of disease. |
| **National Cancer Institute (2013):** Primary Myelofibrosis [9] | Fragestellung: Therapieempfehlungen zur Indikation der Primary Myelofibrosis. |
| | Methodik:<br><br>The PDQ editorial boards use a formal ranking system of levels of evidence to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. For any given therapy, results can be ranked on each of the following two scales: (1) strength of the study design and (2) strength of the endpoints. Together, the two rankings give an idea of the overall level of evidence. Depending on perspective, different expert panels, professional organizations, or individual physicians may use different cut points of overall strength of evidence in formulating therapeutic guidelines or in taking action; however, a formal description of the level of evidence provides a uniform framework for the data, leading to specific recommendations.<br><br>**Ranking system:**<br><br>*1. Randomized controlled clinical trials.*<br>*i. Double-blinded.*<br>*ii. Nonblinded treatment delivery.*<br>*2. Nonrandomized controlled clinical trials.*<br>*3. Case series.*<br>*i. Population-based, consecutive series.*<br>*ii. Consecutive cases (not population-based).*<br>*iii. Nonconsecutive cases.* |
| | **Treatment of anemia**<br><br>▪ Red blood cell transfusion (treatment of decreased red blood cell survival: glucocorticoids)<br>▪ Erythropoietic growth factors<br>▪ Hydroxyurea / Cladribine<br>▪ Thalidomide / Lenalidomide<br>▪ Interferon $\alpha$<br>▪ JAK2 inhibitors: clinical trials<br><br>**Treatment of painful splenomegaly**<br><br>**Temporary treatment**<br>▪ Hydroxyurea: cave: potential leukemogenic effect<br>▪ Interferon $\alpha$: hematologic responses, reduction in spleen size in 30% to 50% of patients (cave: tolerability)<br>▪ Thalidomide / Lenalidomide: favorable responses reported in about 20% to 60% of patients [Level of evidence (LoE): 3iiiDiv]<br>▪ Tipifarnib: response (=transfusion independence or 50% splenomegaly reduction) by $^1/_3$ of 34 symptomatic patients [LoE: 3iiiDiv]<br>▪ JAK2 inhibitors: clinical trials<br>▪ Splenic radiation therapy<br><br>**Splenectomy** |

<table>
<tr><td></td><td>benefits: i.e. symptoms ↓, portal hypertension ↓, red blood cell transfusions ↓, but no benefit for thrombocytopenia)<br><br>benefits: i.e. postoperative mortality of 10% and morbidity of 30% caused by infection, bleeding, or thrombosis, accelerated progression to blast crisis that was seen by some investigators but not others<br><br>Subsequent treatment with Hydroxyurea or Cladribine (alternative for patients with thrombocytosis & hepatomegaly after splenectomy).<br><br>Erläuterungen: The decision to perform splenectomy represents a weighing of the benefits (i.e., reduction of symptoms, decreased portal hypertension, and less need for red blood cell transfusions) versus the debits (i.e., postoperative mortality of 10% and morbidity of 30% caused by infection, bleeding, or thrombosis; no benefit for thrombocytopenia; and accelerated progression to blast crisis that was seen by some investigators but not others).<br><br>Allogeneic peripheral stem cell or bone marrow transplantation(when a suitable sibling donor is available)<br>8% thromboembolism, 7% major hemorrhage in one-half of the patients (retrospective review of 150 patients, with prior cytoreduction and postoperative subcutaneous heparin)</td></tr>
<tr><td rowspan="2">Nodric MPD Study Group (2008): Guidelines for the diagnosis and treatment of patients with polycythemia vera, essential thrombocythemia and primary myelofibrosis. [11]</td><td>Fragestellung: Therapieempfehlungen zur Indikation der PMF</td></tr>
<tr><td>Methodik:<br><br>The Nordic study group on myeloproliferative disorders (NMPD) is a pan-Nordic organisation that has conducted Nordic clinical trials since 2001. NMPD decided in 2006 to write new guidelines, based on already existing national guidelines from the Nordic countries, Italy and Great Britain. The first version was published in 2007. The aim has been to write a document that can be used in all Nordic countries. We have strived to use evidence-based medicine, i.e the conscientious, explicit, and judicious use of current best evidence in making decisions on our recommendations. However, it should be stressed that few randomized controlled trials exist in the MPDs to support decision-making for individual patients. The guidelines are written for health professionals with a speciality or interest in haematology. They have now been updated in 2008, incorporating the new diagnostic criteria established by the World Health Organization.<br><br>Grading system:<br>A) Levels of evidence
<table>
<tr><th>Level</th><th>Type of evidence</th></tr>
<tr><td>Ia</td><td>Evidence obtained from meta-analysis of randomised trials</td></tr>
<tr><td>Ib</td><td>Evidence obtained from at least one randomised controlled trial</td></tr>
<tr><td>IIa</td><td>Evidence obtained from at least one well-designed controlled study without randomisation</td></tr>
<tr><td>IIb</td><td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td></tr>
<tr><td>III</td><td>Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies</td></tr>
<tr><td>IV</td><td>Evidence obtained from expert committee reports and/or clinical experiences of respected authorities</td></tr>
</table></td></tr>
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**B) Grades of recommendation**

| Grade | Evidence level | Recommendation |
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| A | Ia, Ib | Required: At least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation |
| B | IIa, IIb, III | Required: Availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation |
| C | IV | Required: Evidence obtained from expert committee reports or opinions and /or clinical experiences of respected authorities.<br>Indicates absence of directly applicable studies of good quality |

Spleen and lung irradiation

Several reports have documented that radiation of the spleen may benefit symptomatic patients with huge spleens. However, the risk of ensuing prolonged and severe cytopenias is considerable, probably also due to an effect on circulating progenitor cells. The improvement of symptoms is in most patients but temporary lasting 6-8 months. Radiation of the spleen prior to splenectomy is associated with an increased risk of postoperative bleeding. Radiation of the lungs (whole-lung external beam radiotherapy in a single fraction of 100 cGy) may induce marked clinical improvement and decrease in pulmonary artery systolic pressure in patients with pulmonary hypertension due to myeloid metaplasia.

Recommendations: Spleen irradiation should be considered in elderly patients with symptomatic splenic enlargement, refractory to conventional cytoreductive therapy, and not candidates for splenectomy. Lung irradiation may be used to alleviate symptoms of pulmonary hypertension consequent to myeloid metaplasia in the lungs. (Grade B recommendations, evidence level III).

In addition to mechanical discomfort a massively enlarged spleen is associated with portal hypertension and a hyperdynamic portal flow, implying an increased risk of bleeding from the upper gastrointestinal tract. Furthermore, the enlarged spleen contributes to the development of anaemia and thrombocytopenia consequent to pooling and sequestration of red blood cells and platelets. All these features of hypersplenism is alleviated by splenectomy with symptomatic improvement in most patients and a rise in Hb-concentration in about half of the patients. Accordingly, main indications for splenectomy in PMF include – in addition to pronounced mechanical discomfort - episodes of upper gastrointestinal bleeding secondary to portal hypertension (varices), transfusion-dependent anaemia and low platelet counts. Since the procedure is associated with significant morbidity (infection, thrombosis and bleeding - about 25-30%) and mortality (7-10%) (187,188) conditioning and timing of the patient and surgeon are of utmost importance. There is no evidence in the literature to support the contention, that splenectomy is followed by an increased risk of leukemic transformation (188). Splenectomy prior to SCT in patients with huge spleens is a matter of debate.

Recommendations: Splenectomy should be considered in patients with huge splenomegaly associated with repeated upper gastrointestinal bleeding episodes due to portal hypertension and/or cytopenias secondary to haemodilution, splenic pooling and sequestration of blood cells. (Grade B recommendations, evidence level III).

| Empfehlung zur Therapie der ET und PV | |
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| **Cancer care Ontario (CCO), 2008:** The management of malignant thrombocytosis in Philadelphia Chromosome-negative Myeloproliferative Disease: Guideline recommendations.[8] | Fragestellung: This evidence summary was developed to provide information to aid clinicians in the management of patients with essential thrombocythemia (ET) and polycythemia vera (PV). The following questions were addressed:<br>*1. Is there a definable subgroup of patients who are at a high risk of either thrombosis or bleeding?*<br>*2. Does controlling the platelet count with cytoreductive agents improve clinical outcomes such as overall survival, major and minor thrombosis, hemorrhage, and the development of myelofibrosis?*<br>*3. Does cytoreductive therapy produce additional transformation to acute leukemia (AL)?*<br>*4. What effect does aspirin therapy have on the occurrence of thrombosis or hemorrhage?* |
| | Methodik:<br>The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (6). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by three members of the PEBC Hematology Disease Site Group (DSG) and methodologists.<br>The systematic review is a convenient and up-to-date source of the best available evidence on the management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease. The body of evidence in this review is primarily comprised of mature randomized controlled trial (RCT) data; lesser quality data were also considered. That evidence forms the basis of a clinical practice guideline developed by the Hematology DSG (see Section 1). The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.<br>Systematische Literaturrecherche bis 2007<br>*Hinweis*: The review of cytoreductive therapy (Questions 2 and 3) was restricted to RCTs only. Due to the lack of RCTs investigating risk factors (Question 1) and aspirin therapy (Question 4), additional study designs such as prospective (e.g., cohort and case series) and retrospective (e.g., cohort or case audit studies) studies were located and included. |
| | **RECOMMENDATIONS**<br>• *All ET and PV patients with thrombocytosis should be managed with low-dose aspirin. Special precautions should be taken in the case of patients with greater bleeding risk, or allergies..*<br>• *Management without cytoreductive therapy is a reasonable option for asymptomatic patients.*<br>• *Cytoreductive therapy should be considered as an option for patients with thrombocytosis who have thrombosis. Hydroxyurea is the preferred agent and should be administered to maintain a platelet count of less than 600 x 109/L.*<br>• *If treatment with hydroxyurea is not appropriate, then either interferon or anagrelide are options. Physicians who choose anagrelide to reduce the* |

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| | *risk of arterial thrombosis should be aware that there are data to suggest that it is inferior to hydroxyurea, and its efficacy in comparison to no cytoreductive therapy has not been established. Other than reducing the platelet count, interferon is of unknown efficacy.*<br><br>**Evidenzbasis:**<br>No systematic reviews were retrieved.<br><br>*Outcomes of Cytoreductive Therapy to Control Platelet Count:*<br>Data from six RCTs contributed to our evaluation of outcomes of cytoreductive therapy used to control platelet counts. Two studies, one of patients with ET and one of patients with PV, compared cytoreductive therapy against no cytoreductive therapy. The other studies compared hydroxyurea against various cytoreductive agents: interferon (IFN) and anagrelide in 'high-risk' patients with ET, 32P in older patients with PV, and pipobroman in younger patients with PV. The assessed outcomes included events of thrombosis or hemorrhage, the occurrence of myelofibrosis, and overall survival. The overall quality of the RCTs was on average moderate.<br><br>*Outcomes of Aspirin Therapy:*<br>Three prospective studies assessed the effect of aspirin therapy on thrombosis or bleeding rates in patients with PV. Two of these studies were RCTs, while the other was a non-randomized cohort study.<br>Zwei Studien wurden frühzeitig beendet aufgrund von 'inadequate recruitment' und 'no treatment effect (no reduction in thrombosis under aspirin)'.<br><br>***Question 2: Does controlling the platelet count with cytoreductive therapy improve overall survival, major and minor thrombosis, hemorrhage, or myelofibrosis in patients with ET or PV?:***<br><br>**Thrombosis**<br><br>***Essential Thrombocythemia:***<br><br>Three RCTs examined cytoreductive therapy in patients with ET and reported on the incidence of thrombosis.<br><br>**Cortelazzo et al RCT** compared hydroxyurea against no treatment and followed 114 patients with ET for a median duration of just over six years. The authors found that the occurrence of thrombotic complications was significantly less in the hydroxyurea group in comparison with the no cytoreductive-treatment group (9% vs. 45%, respectively; odds ratio [OR]= 0.12; 95% confidence interval [CI], 0.04 to 0.35).<br><br>**MRC PT1 RCT** compared anagrelide with aspirin or acetylsalicylic acid (ASA) to hydroxyurea with ASA for a median follow-up of over three years and found arterial thrombotic events were more common in the anagrelide arm (OR=2.16; 95% CI, 1.27 to 3.69). However, there were no significant differences in stroke, unstable angina, or myocardial infarction between the treatment arms, and most of the observed difference in total arterial thrombosis was accounted for by a lower incidence of transient ischemic attacks in the hydroxyurea arm. Venous thromboembolism was less common in the anagrelide group (OR=0.27; 95% CI, 0.11 to 0.71).<br><br>**German ET-Study** randomized 55 patients to either hydroxyurea or IFN and observed for a median follow-up of 6.6 years. Rates of thrombotic complications were slightly higher in the hydroxyurea arm (3.5% per 100 patient years vs. 3.2% per 100 patient years, $p$ = 0.026). This small trial is not yet published, and a substantial number of patients (50%) |

withdrew from the IFN arm.

***Polycythemia Vera:***

Three RCTs reported on the incidence of thrombosis in patients with PV receiving cytoreductive agents

**French Polycythemia Study Group (FPSG)** reported on two separate trials in 1997, one of elderly patients (n=461) involving hydroxyurea against 32P and the other of younger patients (n=292) involving pipobroman against hydroxyurea (<65 years). In the former trial, at 15 years of follow-up, rates of major 'vascular events' did not differ significantly between hydroxyurea and 32P treated patients (47% vs. 45%, log-rank test result not reported). In the latter trial, at 14 years of follow-up, rates of major thrombosis were 26% in each treatment arm (log-rank test result not reported).

**The PVSG-01 trial** randomized patients (n=431) between 1969 and 1974 to no treatment (i.e., phlebotomy), 32P, or chlorambucil. At 13 years follow-up (median 5-6 years), thrombosis rates varied from 31%, to 25% and 20%, respectively (no statistical comparison reported), and were lower in the treated arms.

**Hemorrhage**

***Essential Thrombocythemia:***

Bleeding-related outcomes were reported in three RCTs of patients with ET.

**MRC PT1 RCT**, bleeding events were observed in both the anagrelide and hydroxyurea arms (5% and 2% of patients, respectively) but were significantly more common in the anagrelide arm (OR=2.61; 95% CI, 1.27 to 5.33). Hydroxyurea was not shown to be superior to no treatment in terms of bleeding.

**Cortelazzo et al RCT** comparing hydroxyurea and no treatment, the number of hemorrhagic events did not differ significantly between arms (2% vs. 7%, respectively, $\chi 2$=1.8, Fisher's exact test, $p$ = 0.36), and were generally infrequent and minor overall.

**unpublished German ET-Study RCT** reported no major bleed events during follow-up.

***Polycythemia Vera***

No study involving patients with PV reported data for bleeding-related outcomes.

**Myelofibrosis**

***Essential Thrombocythemia:***

None of the studies retrieved in this review provided data regarding the incidence of myelofibrosis in untreated patients with ET.

In comparison with anagrelide treatment, hydroxyurea was associated with statistically lower rates of myelofibrosis in one trial (4% vs. 1%; OR= 2.92; 95% CI, 1.24 to 6.86), though for either agent overall rates of myelofibrosis were low.

***Polycythemia Vera:***

Evidence pertaining to the incidence of myelofibrosis in untreated patients retrieved in this review was of limited value.

Some patients enrolled in the **PVSG-01 RCT** were assigned to receive phlebotomy only, and, in this group, the incidence of myelofibrosis was

10% (and not different from comparison treatment arms), but a substantial number (22%) of these phlebotomy patients later crossed over to chemotherapy arms of that trial.

Among treated patients with PV, hydroxyurea was associated with higher rates of myelofibrosis in comparison with 32P and pipobroman **in two studies**. In the **Najean et al study of older** patients, the incidence of myelofibrosis was 32% in patients treated with hydroxyurea and 32P versus 15% in the 32P-treated. In the **Najean et al study of younger patients**, rates were 17% in the hydroxyurea-treated and 2% in the pipobroman-treated.

**Overall Survival**

Five of six RCTs reported on overall survival; no significant differences between treatment arms were reported in any trial.

***Question 3: Does cytoreductive therapy increase transformation to acute leukemia (AL) in ET or PV?***

***Essential Thrombocythemia:***

Two RCTs examined the effects of cytoreductive therapy on the incidence of acute AL.

**Cortelazzo et al RCT** comparing hydroxyurea to no treatment found a significantly higher incidence of malignancy in the hydroxyurea arm (13% vs. 1.7%, $p = 0.03$) at a median six years of follow-up. In total, eight patients developed malignancies: seven in the treatment group (13%) (two AML, two myelodysplastic syndrome [MDS], two lung, and one chronic lymphocytic leukemia [CLL]), and one (1.7%, breast) in the no-treatment group. The authors reported that fifteen patients in this trial had received prior busulphan and conducted an additional subanalysis on the basis of prior treatment. When patients were analyzed by prior treatment received, five of 15 (33%) patients who received both busulphan and hydroxyurea developed a malignancy, versus three of 77 (3.9%) who received hydroxyurea alone, and none of the 20 (0%) who received no prior treatment. **MRC PT1 RCT** comparing hydroxyurea and anagrelide in patients receiving aspirin reported very little transformation to acute leukemia (1.2%) at 3.3 years follow-up, with no significant differences between arms (1.5% vs. 1%, $p = 0.55$).

***Polycythemia Vera:***

Three RCTs reported on the rates of leukemogenesis with cytoreductive treatment.

**Najean et al RCT** that examined elderly patients by comparing hydroxyurea and 32P in combination against 32P as a single agent found a statistically significant higher incidence of leukemic transformation in the combination arm at 15 years follow-up (31% vs. 23%, respectively, $p < 0.05$) (18). The PVSG-01 RCT found a significantly higher rate of leukemogenesis in treated patients (10%-13.5%, vs. 2%, respectively, $p < 0.05$) over a follow-up ranging from 11 to 18 years.

**Najean et al RCT** comparing hydroxyurea against pipobroman in younger patients reported similar rates of leukemogenesis in both arms (10%, log-rank test, $p > 0.30$) at 14 years follow-up.

***Question 4: What effect does aspirin therapy have on the risk of major thrombosis or hemorrhage?***

***Essential Thrombocythemia:***

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| | No RCTs reported on the effects of aspirin in patients with ET.<br><br>**A single retrospective chart audit study** (n=68) found that patients treated with aspirin (either alone or in combination with cytoreductive therapy, n=57) had a lower incidence of thrombosis in comparison to those who did not receive aspirin (n=11) (2.8 vs. 20.7 events/100 patient years, respectively).<br><br>***Polycythemia Vera:***<br><br>Three studies, two RCTs and one prospective trial, investigated the use of aspirin therapy in PV.<br><br>**ECLAP RCT** comparing low-dose aspirin (100 mg/day) against no aspirin in patients receiving cytoreductive therapy, the risk of the primary combined end point of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes was significantly reduced in the aspirin arm (RR=0.40; 95% CI, 0.18 to 0.91; $p$ = 0.03).<br><br>**PVSG-05 RCT** compared high-dose aspirin (900 mg/day) against cytoreductive therapy directly and found that aspirin was not superior to cytoreductive therapy in reducing the risk of thrombosis (in fact, the risk was slightly, though not significantly, elevated in the aspirin group, with 7/83 vs. 2/83 patients affected, respectively, $p$ > 0.05)<br><br>**One additional small non-randomized prospective study** of aspirin in PV patients (n=159) was retrieved in abstract form and supported the findings of the ECLAP study. In this study, patients received phlebotomy or cytoreductive therapy and either aspirin or no aspirin. Thrombosis was less common in the patients who received aspirin (OR=0.6, significance level not reported), and hemorrhagic events were more common (25 events for ASA vs. five events for no ASA, risk value not reported). |
| **Reilly et al. 2012:** Guideline for the diagnosis and management of myelofibrosis [13] | Fragestellung: The purpose of this guideline is to provide a practical, rather than a research, approach to the diagnosis, investigation and management of patients with primary, as well as post-polycythaemic myelofibrosis (post-PV MF) and post-thrombocythemic myelofibrosis (post-ET MF). |
| | Methodik: The criteria used to state levels and grades of evidence are as outlined in the Procedure for Guidelines commissioned by the BCSH; the 'GRADE' system was used to score strength and quality of evidence. |
| | Strength of recommendations<br>*Strong (grade 1)*: Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.<br>*Weak (grade 2)*: Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.<br>Quality of evidence<br>The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.<br>(A) *High:* Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.<br>(B) *Moderate:* Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).<br>(C) *Low*: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion. |

**Treatment:**

Recommendations: medical management of splenomegaly

*First Line:*

- Hydroxycarbamide (in the absence of cytopenias).
  *Evidenzstatement: 'This is the most widely used agent, despite limited published data supporting its efficacy'*
- Thalidomide and prednisolone (in presence of cytopenias)
  – consider lenalidomide (if anaemic with platelet count >100 9 109/l).
  *Evidenzstatement: 'Immunomodulatory drugs have been evaluated in a number of small studies'*

*Second Line:*

- Consideration should be given to the use of JAK inhibitors either as part of a clinical trial, or via patient access protocols. These agents are now approved in the USA for first line therapy which is appropriate following approval **(Evidence level 1, Grade A)**.
  *Evidenzbasis: JAK inhibitors may have a future role in the anagement of splenomegaly (see 'Novel Therapies' section) and are the only therapies to have been evaluated in the context of randomized clinical trials.*

Recommendations for splenectomy

*Evidenzstatement: The place of splenectomy in the management of myelofibrosis is well established. Routine splenectomy is inappropriate and the procedure should be restricted to carefully selected patients with refractory haemolysis, symptomatic splenomegaly, significant splenic infarction, severe portal hypertension and severe hypercatabolic symptoms.*

*Indications*

- Drug-refractory symptomatic splenomegaly.
- Drug-refractory anaemia.
- Symptomatic portal hypertension (e.g. ascites, bleeding varices).
- Severe catabolic symptoms including cachexia
  **(Evidence level 2, Grade C).**

*Peri-operative management*

- Evaluate cardiac, hepatic, renal and metabolic status.
- Correction of any coagulopathy.
- Meticulous control of platelet count pre- and post-splenectomy.
- Laparoscopic splenectomy not advised.
- Splenic artery embolization not advised.
- Appropriate vaccination and long-term penicillin
  **(Evidence level 2, Grade C).**

*Post-splenectomy myeloproliferation*

- Cytoreductive therapy (hydroxycarbamide). Cladribine can be considered in selected patients **(Evidence level 2, Grade C).**

Recommendations for radiotherapy

- Patients with symptomatic splenomegaly, who have an adequate platelet count (>50 3 109/l) and who are not deemed suitable for surgical intervention. Platelet transfusions may be required post-treatment.
- EMH involving vital organs.
- Severe bone pain **(Evidence level 2, Grade C).**
  *Evidenzstatement: Radiotherapy is a valuable alternative to splenectomy in patients with symptomatic splenomegaly and an adequate platelet count (>50 9 109/l) and in whom surgery is deemed unsuitable. However, while symptomatic relief, with mild to moderate reduction in spleen size, occurs in the majority of cases, the response is only short lived.*

*Radiotherapy is a valuable alternative to splenectomy in patients with symptomatic splenomegaly and an adequate platelet count (>50 9 109/l) and in whom surgery is deemed unsuitable. In the Mayo Clinic experience, a median radiation dose of 277 cGy was administered in a median of 7•5 fractions. Reduction in spleen size was noted in the majority of cases and lasted for a median of 6 months, although 44% experienced cytopenias, of which 13% were fatal. Median survival after irradiation was 22 months. A subsequent study administered a median of 980 cGy with a response rate of 59% and a median duration of response of 10 months. A case report suggested that low-dose intermittent radiation, e.g.100 cGy, every 1–3 months, might be a reasonable approach to control post-splenectomy, hepatomegaly symptoms.*

Recommendations for myelosuppressive therapy

- Hydroxycarbamide is the first line choice for the control of the hyperproliferation manifestations of myelofibrosis **(Evidence level 2, Grade B).**
- Anagrelide should be used with caution in patients with established MF **(Evidence level 2, Grade B).**
- Use of IFN-a in PMF patients should be restricted to cases with early phase disease with more proliferative disease features **(Evidence level 2, Grade B).**
- High starting doses of conventional IFN-a are very poorly tolerated in PMF and should be avoided. When conventional IFN-a is used, it is recommended to commence at 1·5 million units three times per week and increase to a maximum of 15 million units/week as tolerated. If using pegylated-IFN, a2a is the recommended agent **(Evidence level 2, Grade B).**

  *Evidenzstatement: Myelosuppressive therapy in PMF is not curative and there are relatively few published series, most of which are small, non-randomized and incorporate different definitions of response.*

Recommendations for Allo-HSCT

Definition: A transplant–eligible patient is defined as one deemed fit enough to undergo the procedure with manageable co-morbidities and having an HLA-matched sibling or unrelated donor available.

- Transplant-eligible patients <45 years of age, with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic abnormalities, should be considered for MA allo-HSCT **(Evidence level 2, Grade C).**
- Transplant-eligible patients with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic abnormalities, together with an HSCT co-morbidity index 3, or who are aged over 45 years, should be considered for RIC allo-HSCT **(Evidence level 2, Grade C).**
- Patients should be transplanted before they have received more than 20 units of red cells **(Evidence level 2, Grade C).**
- Use of oral busulfan should be accompanied by targeted dosing according to plasma levels. Alternatively, intravenous busulfan can be used, guided by plasma levels where possible **(Evidence level 2, Grade C).**
- There is no convincing evidence for pre-transplant splenectomy and some evidence of harm both from surgical morbidity and mortality and a possible increased risk of relapse post-transplant **(Evidence level 2, Grade C).**
- JAK2 V617F mutated patients monitored by quantitative polymerase

chain reaction (Q-PCR) post-transplant who do not achieve or who relapse from molecular CR are candidates for donor lymphocyte infusions in the absence of GvHD **(Evidence level 2, Grade B)**. The role of Q-PCR for other mutations post-bone marrow transplantation remains unclear.

- There is no conclusive evidence to support use of a specific MA or RIC conditioning regimen, although favourable results have been achieved following BUCY and FLUBU and anti-lymphocyte globulin. Every effort should be made to enrol patients in prospective clinical studies and data should be reported to National and International Registries **(Evidence level 2, Grade C).**

Recommendations novel therapies

- A number of JAK inhibitors are at various stages of clinical development and a consistent pattern of response in splenomegaly and disease-related symptoms is emerging. Initial data from a Phase III study suggests survival may be improved. Further data with regards to effects upon survival and leukaemic transformation are awaited. Current recommendation to consider referring patients, who have failed hydroxycarbamide therapy and are not presently suitable for BMT, for trials with JAK inhibitors (Evidence level 1, Grade A). Should these agents be approved then they would be considered as first-line agents for patients with troublesome splenomegaly and disease-related symptoms **(Evidence level 1, Grade A).**

**Treatment of anaemia**

Blood transfusion

As with most clinical scenarios, the efficacy of blood transfusion in PMF has not been proven, nor has its efficacy been subjected to evaluation by a randomized trial. Nevertheless, blood transfusion is standard therapy for symptomatic patients and should be assessed individually. Regular transfusions will eventually lead to iron overload, although it remains unclear whether this leads to toxicity and end-organ damage. Indeed, hyperferritin-aemia has not been shown to affect survival in patients with PMF. As a result, chelation therapy is not routinely recommended. This may not be true for patients receiving an allogeneic transplant, where improved survival was observed in patients who had received <20 units of red blood cells.

Transfusion recommendations

- Red cell transfusions are recommended in PMF patients with symptomatic anaemia **(Evidence level 2, Grade B)**.
- Iron chelation therapy is not routinely recommended in PMF **(Evidence level 2, Grade B)**.

Erythropoietin

The efficacy of recombinant human erythropoietin (rEPO) appears to be limited principally to a subgroup of patients with inappropriately low endogenous EPO levels in the face of relatively moderate anaemia. The reported experience with rEPO in PMF has generally been limited to small case series, the interpretation of which is confounded by non-uniform response criteria, varying rEPO dosing regimens and a range of concomitant therapies.

Recommendations for erythropoietin

- A trial of recombinant erythropoietin therapy should be considered in anaemic PMF patients with inappropriately low erythropoietin levels (<125 u/l). Responses are more likely in those with relatively moderate anaemia **(Evidence level 2, grade B).**

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| | • rEPO should be commenced at a dose of 10 000 units three times weekly (or darbepoietin 150 lg weekly), doubling to 20 000 three times weekly (darbepoietin 300 lg weekly) after 1–2 months in the absence of an early response. Treatment should be discontinued after 3–4 months if no response occurs **(Evidence level 2, grade B).** |
| **Empfehlung zur Therapie der ET, PV, PMF** | |
| **NCI, 2013:** Chronic Myeloproliferative Disorders Treatment [9] | Fragestellung: Therapiempfehlungen zur Indikation der ET, PV, PMF |
| | Methodik:<br>The PDQ editorial boards use a formal ranking system of levels of evidence to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. For any given therapy, results can be ranked on each of the following two scales: (1) strength of the study design and (2) strength of the endpoints. Together, the two rankings give an idea of the overall level of evidence. Depending on perspective, different expert panels, professional organizations, or individual physicians may use different cut points of overall strength of evidence in formulating therapeutic guidelines or in taking action; however, a formal description of the level of evidence provides a uniform framework for the data, leading to specific recommendations.<br>**Ranking system:**<br>*1. Randomized controlled clinical trials.*<br>*i. Double-blinded.*<br>*ii. Nonblinded treatment delivery.*<br>*2. Nonrandomized controlled clinical trials.*<br>*3. Case series.*<br>*i. Population-based, consecutive series.*<br>*ii. Consecutive cases (not population-based).*<br>*iii. Nonconsecutive cases.* |
| | **Polycythemia Vera**<br>Treatment Overview:<br>The primary therapy for p. vera includes intermittent, chronic phlebotomy to maintain the hematocrit below 45%, and this recommendation has been confirmed in a randomized, prospective trial, which demonstrated lower rates of cardiovascular death and major thrombosis using this hematocrit target. The target level for women may need to be lower (e.g., hematocrit <40%), but there are no empiric data to confirm this recommendation.<br>In addition, progressive splenomegaly or pruritus not controllable by antihistamines may persist despite control of the hematocrit by phlebotomy. If phlebotomy becomes impractical, hydroxyurea or interferon-alpha can be added to control the disease.<br>Treatment options:<br>1. Phlebotomy.<br>2. Hydroxyurea (alone or with phlebotomy).<br>3. Interferon-alpha and pegylated interferon-alpha.<br>4. Rarely, chlorambucil or busulfan may be required, especially if interferon or hydroxyurea are not tolerated, as is often seen in patients older than 70 years.<br>5. Low-dose aspirin (≤100 mg) daily, unless contraindicated by major bleeding or gastric intolerance. |

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| | *Evidenz: The Polycythemia Vera Study Group randomly assigned more than 400 patients to phlebotomy (target hematocrit <45), radioisotope phosphorous-32 (2.7 mg/m2 administered intravenously every 12 weeks as needed), or chlorambucil (10 mg administered by mouth daily for 6 weeks, then given daily on alternate months). The median survival for the phlebotomy group (13.9 years) and the radioisotope phosphorous-32 group (11.8 years) was significantly better than that of the chlorambucil group (8.9 years), primarily because of excessive late deaths from leukemia or other hematologic malignancies.**[Level of evidence: 1iiA]** Because of these concerns, many clinicians use hydroxyurea for patients who require cytoreductive therapy that is caused by massive splenomegaly, a high phlebotomy requirement, or excessive thrombocytosis.*<br><br>*In a pooled analysis of 16 different trials, interferon-alpha therapy resulted in avoidance of phlebotomy in 50% of patients, with 80% of patients experiencing marked reduction of splenomegaly.**[Level of evidence: 3iiiDiv]** Interferon posed problems of cost, side effects, and parenteral route of administration, but no cases of acute leukemia were seen in this analysis. When patients are poorly compliant with phlebotomy or issues of massive splenomegaly, leukocytosis, or thrombocytosis supervene, treatment with interferon or pegylated interferon is considered for patients younger than 50 years (who are more likely to tolerate the side effects and benefit from a lack of transformation to leukemia), while hydroxyurea is considered for patients older than 50 years.*<br><br>*In a Cochrane review of two randomized studies of 630 patients (siehe CC Reviews) with no clear indication or contraindication for aspirin, those receiving 100 mg of aspirin versus placebo had reduction of fatal thrombotic events, but this benefit was not statistically significant (odds ratio, 0.20; 95% CI, .03–1.14).*<br><br>*A retrospective review of 105 patients who underwent surgery documented 8% thromboembolism and 7% major hemorrhage with prior cytoreduction by phlebotomy and postoperative subcutaneous heparin in one half of the patients.*<br><br>**Primary Myelofibrosis**<br><br>Treatment Overview<br>Asymptomatic low-risk patients (based on the aforementioned prognostic systems) should be followed with a watchful-waiting approach. The development of symptomatic anemia, marked leukocytosis, drenching night sweats, weight loss, fever, or symptomatic splenomegaly would warrant therapeutic intervention. The profound anemia that develops in this disease usually requires red blood cell transfusion. Red blood cell survival is markedly decreased in some patients; this can sometimes be treated with glucocorticoids.<br><br>Treatment options:<br>1. Ruxolitinib<br>2. Clinical trials involving other JAK2 inhibitors.<br>3. Hydroxyurea<br>4. Allogeneic peripheral stem cell or bone marrow transplantation<br>5. Thalidomide<br>6. Lenalidomide<br>7. Pomalidomide<br>8. Splenectomy<br>9. Splenic radiation therapy or radiation to sites of symptomatic extra-medullary hematopoiesis (e.g., large lymph nodes, cord compression) |

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| | 10. Cladribine<br>11. Interferon-alpha<br><br>Disease-associated anemia may occasionally respond to the following:<br>• Erythropoietic growth factors. Erythropoietin and darbepoetin are less likely to help when patients are transfusion dependent or manifest a serum erythropoietin level greater than 125 U/L.<br>• Prednisone (40–80 mg/day).<br>• Danazol (600 mg/day).<br>• Thalidomide (50 mg/day) ± prednisone. Patients on thalidomide require prophylaxis for avoiding thrombosis and careful monitoring for hematologic toxicity.<br>• Lenalidomide (10 mg/day) ± prednisone. In the presence of del(5q), lenalidomide with or without prednisone, can reverse anemia and splenomegaly in most patients. However, patients on lenalidomide require prophylaxis for avoiding thrombosis and careful monitoring for hematologic toxicity.<br>• Pomalidomide. Patients on pomalidomide require prophylaxis for avoiding thrombosis and careful monitoring for hematologic toxicity.<br><br>Evidenz:<br>Ruxolitinib: In two prospective, randomized trials, 528 higher-risk patients were randomly assigned to ruxolitinib or to best available therapy or placebo; at 48 weeks, patients on ruxolitinib had a decrease of 40% to 60% in mean palpable spleen length or in spleen volume compared with an increase of 1% to 4% with best available therapy. **[Level of evidence: 1iiDiv]; [Level of evidence: 1iDiv]** Ruxolitinib also improved overall quality-of-life measures with low toxic effects in both studies but with no benefit in overall survival. Discontinuation of ruxolitinib results in a rapid worsening of splenomegaly and recurrence of systemic symptoms.<br><br>Hydroxyurea is useful in patients with splenomegaly but may have a potential leukemogenic effect. In patients with thrombocytosis and hepatomegaly after splenectomy, cladribine has shown responses as an alternative to hydroxyurea. The use of interferon-alpha can result in hematologic responses, including reduction in spleen size in 30% to 50% of patients, though many patients do not tolerate this medication. Favorable responses to thalidomide and lenalidomide have been reported in about 20% to 60% of patients.**[Level of evidence: 3iiiDiv]**<br><br>A response defined as 50% reduction of splenomegaly or development of transfusion independence was attained by one-third of 34 symptomatic patients using tipifarnib.**[Level of evidence: 3iiiDiv]** A more aggressive approach involves allogeneic peripheral stem cell or bone marrow transplantation when a suitable sibling donor is available. Allogeneic stem cell transplantation is the only curative treatment available, but the morbidity and mortality limit its use to younger high-risk patients. Detection of the JAK2 mutation after transplantation is associated with a worse prognosis.<br><br>**Essential Thrombocythemia**<br><br>Treatment Overview:<br><br>Treatment options:<br>1. No treatment, unless complications develop, if patients are asymptomatic, younger than 60 years, and have a platelet count of less than 1,500 × 109/L.<br>2. Hydroxyurea. |

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| | 3. Interferon-alpha or pegylated interferon-alpha.<br>4. Anagrelide.<br><br>Controversy is considerable regarding whether **asymptomatic patients** with essential thrombocythemia require treatment.<br><br>Evidenz:<br>*A randomized trial of patients with essential thrombocythemia and a high risk of thrombosis compared treatment with hydroxyurea titrated to attain a platelet count below 600,000/mm3 with a control group that received no therapy. Hydroxyurea was found to be effective in preventing thrombotic episodes (4% vs. 24%).**[Level of evidence: 1iiDiv]***<br><br>*A retrospective analysis of this trial found that antiplatelet drugs had no significant influence on the outcome. Resistance to hydroxyurea is defined as a platelet count of greater than 600,000/mcL after 3 months of at least 2 g per day of hydroxyurea or a platelet count greater than 400,000/μL and a white blood count of less than 2,500/μL or a hemoglobin less than 10 g/dL at any dose of hydroxyurea.*<br><br>*In a case-controlled observational study of 65 low-risk patients (<60 years of age, platelet count <1,500 × 109/L, and no history of thrombosis or hemorrhage) with a median follow-up of 4.1 years, the thrombotic risk of 1.91 cases per 100 patient years and hemorrhagic risk of 1.12 cases per 100 patient years was not increased over the normal controls.*<br><br>*A prospective, randomized trial of 809 patients compared hydroxyurea plus aspirin with anagrelide plus aspirin. Although the platelet-lowering effect was equivalent, the anagrelide group had significantly more thrombotic and hemorrhagic events (hazard ratio [HR], 1.57; P = .03) and more myelofibrosis (HR, 2.92; P = .01). No differences were seen for myelodysplasia or acute leukemia.**[Level of evidence: 1iiA]***<br><br>*Many clinicians use hydroxyurea or platelet apheresis prior to elective surgery to reduce the platelet count and to prevent postoperative thromboembolism. No prospective or randomized trials document the value of this approach.*<br><br>Among **low-risk patients** (defined as age 60 years or younger with no prior thrombotic episodes), a retrospective review of 300 patients showed benefit for antiplatelet agents in reducing venous thrombosis in JAK2-positive cases and in reducing arterial thrombosis in patients with cardiovascular risk factors. Balancing the risks and benefits of aspirin for low-risk patients can be difficult. In an extrapolation of the data from trials of p. vera, low-dose aspirin to prevent vascular events has been suggested, but there are no data from clinical trials to address this issue. |

**Primärstudien**

| | |
|---|---|
| **Trelinski et al. (2009):** The influence of low-dose aspirin and hydroxyurea on platelet-leukocyte interactions in patients with essential thrombocythemia. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 2009; 20 (8): 646-51.[17] | Studienziel: Effekt von Aspirin und Hydroxyurea (HU) auf die Funktion der Blutplättchen, Leukozyten und der Bildung von Blutplättchen/Leukozyten Konjugaten in Patienten mit einer essentiellen Thrombozythämie<br><br>Vergleich: Aspirin oder HU vs. Placebo<br><br>Endpunkte: Blutmarker (P-Selektin Expression; Blutplättchen/Leukozyten Konjugate)<br><br>Ergebnisse (basierend auf 60 Studienteilnehmer; 40 Patienten vs. 20 gesunde Kontrollen):<br>• **Allgemein:** Patienten wurden eingeteilt in zwei Risikogruppen (Niedrig-Risiko Patienten und Hoch-Risiko Patienten). Alle Niedrig-Risiko Patienten wurden mit Aspirin behandelt, alle Hoch-Risiko Patienten mit HU. *Hinweis: Bei der Ergebniswiedergabe, werden aufgrund des relevanten Anwendungsgebietes nur die Ergebnisse zu den hoch-Risiko Patienten berücksichtigt.*<br>• P-Selektin Expression: Allgemein lagen die Werte in der Gruppe der Patienten mit einer essentiellen Thrombozythämie höher. Es zeigte sich ein stat. signifikanter Anstieg an P-Selektinen nach einer HU Therapie sowohl zum basalen Zeitpunkt ($p<0.001$), als auch nach einer Stimulation mit ADP/Coll ($p<0.001$).<br><br>Bildung von Blutplättchen/Leukozyten Konjugaten: Allgemein lagen die Werte in der Gruppe der Patienten mit einer essentiellen Thrombozythämie höher. Eine Behandlung mit HU führte zu einer stat. signifikanten Abnahme an Blutplättchen/Monozyt Konjugaten (nach einer Stimulation mit ADP/Coll)→ Vorher: 41.67 (27.64-57.40) vs. Nachher: 33.68 (18.15-53.32); $p<0.05$). Es zeigten sich keine stat. signifikanten Unterschiede hinsichtlich der Blutplättchen/Monozyt Konjugaten zum basalen Zeitpunkt und der Blutplättchen/polymorphnuklearen Konjugaten (basal/nach Stimulation mit ADP/Coll). |
| **Harrison et al. (2005):** Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 2005; 353 (1): 33-45.[6]<br><br>*Siehe auch:* ***Cacciola RR, Di FE, Pezzella F, Tibullo D, Giustolisi R, Cacciola E****. Effect of anagrelide on platelet coagulant function in patients with essential thrombocythemia. Acta Haematol 2007; 118 (4): 215-8. [3]* | Population: Patienten mit einer essentiallen Thrombozythämie<br><br>Vergleich: Anagrelid vs. HU *(Hinweis: Alle Patienten erhielten zusätzlich niedrig-dosiertes Aspirin)*<br><br>Endpunkte:<br>• Primärer Endpunkt: Kombinationsendpunkt bestehend aus Risiko einer arteriellen Thrombose (Myokardinfarkt, nicht stabile Angina, Gehirnschäden, transitorische ischämische Attacken, oder peripheren artieriellen Thrombosen), venöse Thrombose (tiefe Venenthrombosen, splanchnischen Venenthrombosen, pulmonale Embolien), schwere Blutungen, oder Tod durch thrombotische bzw. Blutungsursachen<br>• Sekundäre Endpunkte: Zeit bis zum ersten Auftreten eines arteriellen oder thrombotischen Ereignisses, Zeit bis zum ersten Auftreten einer schweren Blutung, Zeit bis zum Tod, Inzidenz einer Umwandlung in einer Thrombose, akute myeloische Leukämie, Myelodysplasie oder Polycythemia vera, Kontrolle der Blutplättchenanzahl<br><br>Ergebnisse:<br>• Kontrolle der Blutplättchenanzahl: Nach 9 Monaten und weitergehen, zeigte sich kein stat. signifikanter Unterschied zwischen den Gruppen. Es zeigte sich lediglich nach 3 und 6 Monaten eine stat. signifikant höhere Anzahl an Blutplättchen in der Anagrelid Gruppe im Vergleich zur HU Gruppe ($p<0.001$). Die mediane Anzahl an weißen Blutkörperchen war ab |

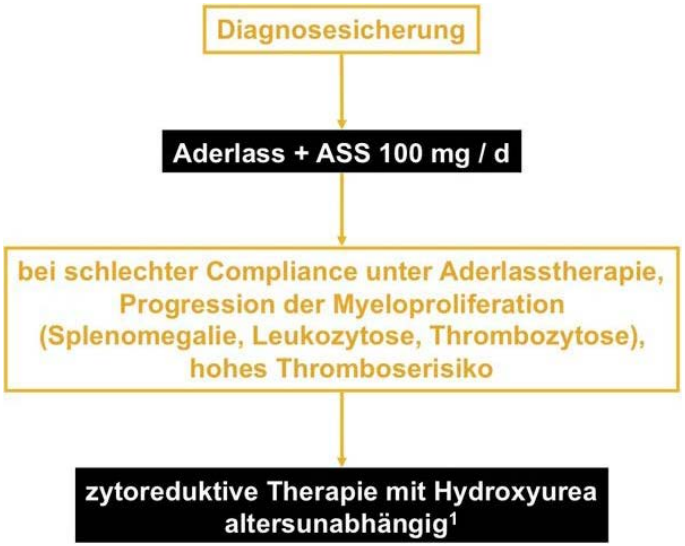
| | |
|---|---|
| | 3 Monaten nach der Randomisierung und weiter bleibend, stat. signifikant niedriger in der HU Gruppe im Vergleich zu der Anagrelid Gruppe (p<0.001).<br>• <u>Vaskuläre Endpunkte</u>:<br>o Es zeigte sich ein stat. signifikant höheres Risiko unter der Anagrelid Gruppe hinsichtlich des primären Kombinationsendpunktes (arterielle oder venöse Thrombosen, schwere Blutungen oder Tod durch vaskuläre Ursachen) (OR: 1.57; 95%KI: 1.04-2.37; p=0.03).<br>o Bei den sekundären Endpunkten zeigte sich zudem ein stat. signifikanter Unterschied zwischen den Interventionen zum Nachteil von Anagrelid. Arterielle Thrombosen traten zweimal häufiger unter der Anagrelid Gruppe auf (OR: 2.16; 95%KI: 1.27-3.69; p=0.004). Es zeigten sich stat. signifikant mehr transitorische ischämische Attacken in der Anagrelid Gruppe (14 vs. 1; OR: 5.72; 95%KI: 2.08-15.73; p<0.001).<br>o Andere Endpunkte traten numerisch, jedoch nicht stat. signifikant, häufiger unter der Anagrelid Gruppe auf.<br>o Zusätzlich zeigte sivh ein stat. signifikanter Anstieg an schweren Blutungen unter Anagrelid (OR: 2.61; 95%KI: 1.27-5.33; p=0.008), darunter stat. signifikant gastrointestinale Blutungen (OR: 1.33; 95%KI: 1.33-9.44; p=0.01).<br>o Gegensätzlich dazu, zeigte sich ein stat. signifikant geringeres Risiko unter Anagrelid hinsichtlich venöser Thromboembolien (OR: 0.27; 95%KI: 0.11-0.71; p=0.006) und tiefe Venenthrombosen (OR: 0.20; 95%KI: 0.06-0.71; p=0.009).<br><br><u>Hinweis:</u> *Die Studie war nicht gepowert um Unterschiede hinsichtlich der Mortalität zu identifizieren.*<br><br>• <u>Entwicklung der Erkrankung</u>: Stat. signifikant erhöhte Rate an einer Myelofibrose-Entwicklung (OR: 2.92; 95%KI: 1.24-6.86; p=0.01), worunter 3/21 Patienten starben (→ alle davon gehörten zu der Anagrelid Gruppe).<br><br>• <u>Sicherheit und unerwünschte Ereignisse</u>:<br>o Stat. signifikant mehr Patienten unter einer Anagrelid Therapie brachen die Studie ab (148 vs. 79; p<0.001). Darunter brachen stat. signifikant mehr Patienten unter der Anagrelid Therapie aufgrund von unerwünschten Nebenwirkungen oder aufgrund dem Eintreten eines Endpunktes bzw. einer Nebenwirkung ab (OR: 88 vs. 43; p<0.001).<br>o Zusätzlich waren die Raten nicht-thrombotischer kardiovaskulärer Ereignisse, gastrointestinaler Ereignisse, nicht-kardialen Ödeme, Kopfschmerzen stat. signifikant höher unter der Anagrelid Therapie.<br>o Gegensätzlich zeigte sich, dass dermatologische Nebenwirkungen stat. signifikant häufiger unter der Therapie mit HU auftraten (keine allgemein stat. Zahl gegeben).<br><br>***<u>Unterschied Ergebnisse Studie von Harrison (2005) vs, Cacciola (2007):</u>***<br>*→ In Harrison 2005 zeigte sich ein vermehrtes Auftreten an Thrombosen und Blutungen unter einer Therapie mit Anagrelid plus Aspirin. In der Studien von Cacciola 2007 zeigte sich unter derselbigen Therapie eine Noramlisierung der Blutplättchenfunktion, wenn gegen HU plus Aspirin verglichen wurde.* |

| | |
|---|---|
| **Kiladjian et al. (2005):** Long-term incidence of hematological evolution in three French prospective studies of hydroxyurea and pipobroman in polycythemia vera and essential thrombocythemia. [Review] [42 refs]. Seminars in Thrombosis & Hemostasis 2006; 32 (4 Pt 2): 417-21. [7] | 1980 initiierte randomisierte Studie zur Behandlung von Polycythemia Vera mit Hydroxyurea und Pipobroman → finale Resultate<br><br>Population: Patienten <65 Jahre mit einer Polycythemia vera<br><br>Vergleich: HU vs. Pipobroman<br><br>Endpunkte: Gesamtüberleben, Entwicklung zu akute myeloische Leukämie (AML)/ myelodysplastische Syndrom (MDS) und Myelofibrose (MF), Vaskuläre Ereignisse<br><br>Ergebnisse:<br>• Gesamtüberleben: Das mediane Gesamtüberleben der vollständigen Kohorte lag bei 17 Jahren (95%KI:15.4-19.4 Jahre). Stat. signifikanter Unterschied zwischen den Behandlungen zum Vorteil von HU (HR: 20.3 Jahre (95%KI: 16.4-25.0 Jahre) vs. HR: 15.4 Jahre (95%KI: 13.4-17.0 Jahre); p=0.008). Dieses Ergebnis blieb auch nach der Auswertung der follow-up Daten stat. signifikant (p=0.026).<br><br>*Hinweis: 21% der Patienten bekamen beide Behandlungen (durch Therapiewechsel). Ein Wechsel von einer HU Behandlung zu einer Behandlung mit Pipobroman, erhöhte stat. signifikant das Mortalitäts-risiko (HR: 2.06; 95%KI: 1.09-3.87; p=0.26), wenn verglichen wird mit Patienten die weiterhin mit HU behandelt wurden. Umgekehrt wurde das Risiko nicht erhöht (Switch: Pipobroman → HU).*<br><br>• Entwicklung zu AML/MDS und MF:<br>o Nach 10, 15 und 20 Jahren, war die kumulative Inzidenz einer AML/MDS, bei der vollständigen Kohorte, statistische signifikant unterschiedlich zwischen einer Behandlung mit HU (6.6%, 16.5% und 24.2 %) und einer Behandlung mit Pipobroman (13.1%, 34.1% und 52.1%; p=0.004).<br><br>o Die kumulative Inzidenz einer Myelofibrose nach 10.15 und 20 Jahren, war stat. signifikant unterschiedlich mit 15.5%, 24.3% und 31.6% unter einer Behandlung mit HU (94 Patienten) vs. 5.1%, 9.8% und 21.3% unter einer Behandlung mit Pipobroman (130 Patienten) (p=0.02).<br>o Patienten die in der vollständigen follow-up Periode nur eine Behandlung bekamen, zeigten eine stat. signifikant unterschiedliche kumulative Inzidenz der AML/MDS nach 10,15 und 20 Jahren (HU: 7.3, 10.7 und 16.6% vs. Pipobroman: 14.6%, 34% und 49.4%; p=0.002).<br><br>Vaskuläre Ereignisse: Keine stat. signifikanten Unterschiede zwischen den Interventionen. |

Gemeinsamer Bundesausschuss

**Anlage I: Algorithmen zum therapeutischen Vorgehen (Quelle: DGHO)**

**Polycythaemia Vera**

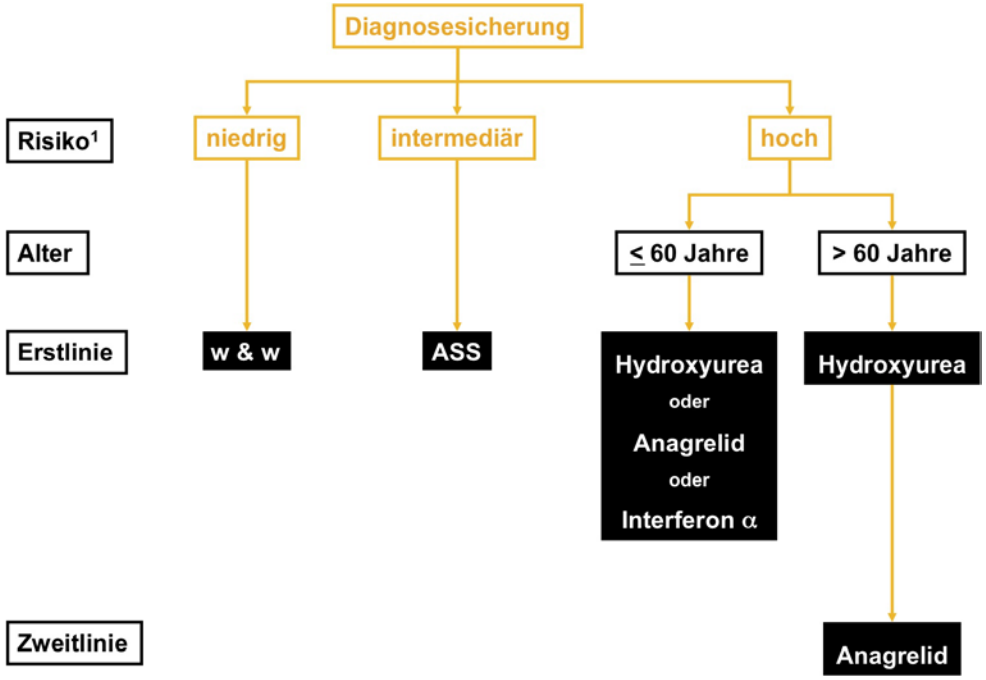



[1]Alternativen: bei Patienten < 40 a: (Peg)Interferon α

bei Patienten > 75 a: Busulfan / $P^{32}$ / (Pipobroman - nicht in D)

w & w = watch & wait
sorgfältige Überwachung hinsichtlich Übergang in höhere Risikogruppe

**Essentielle Thrombozythämie**



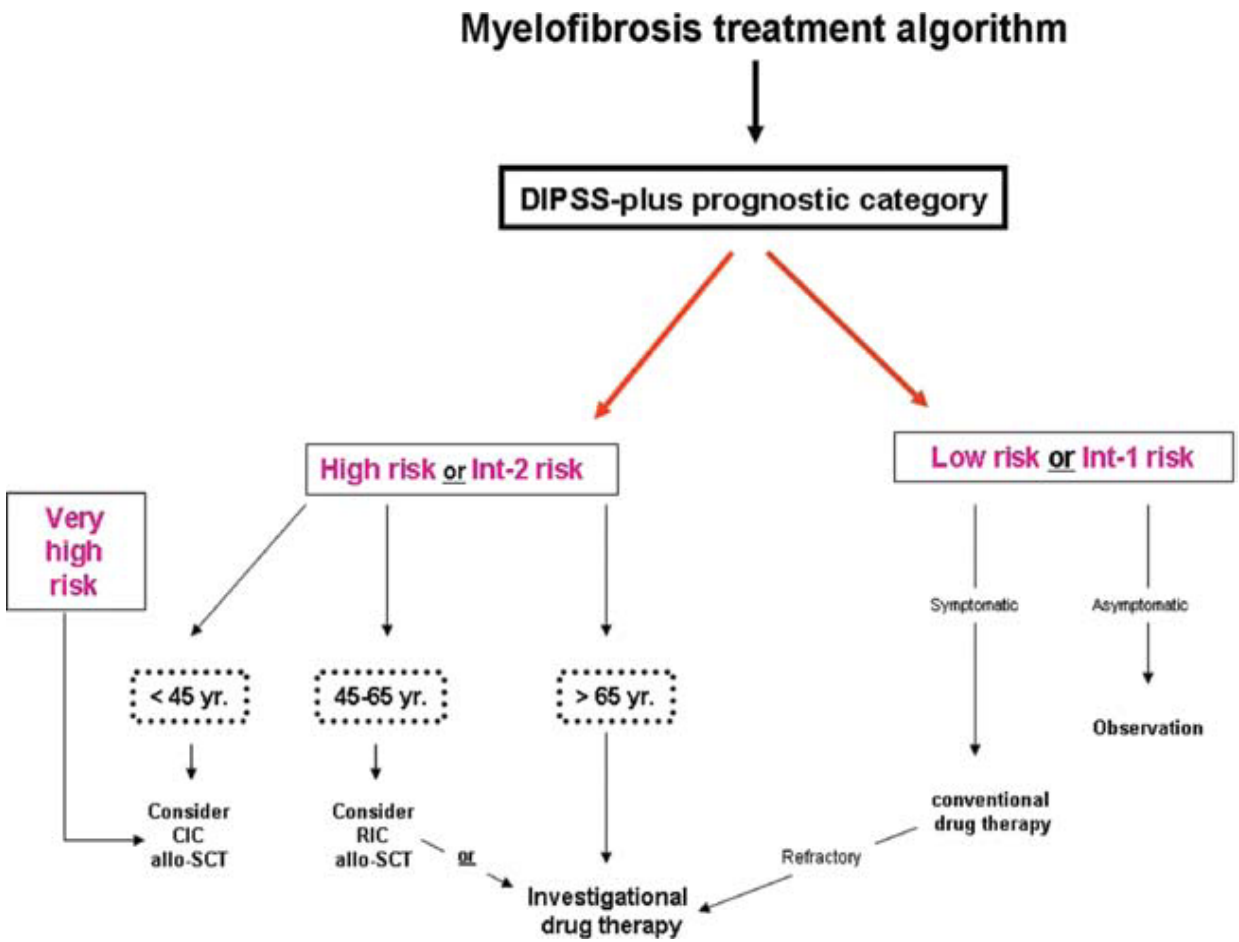

[1]**Niedrigrisiko-Patienten:** außer Mikrozirkulationsstörungen keiner der Hochrisiko-Faktoren

**Intermediärrisiko-Patienten: v**askuläre Risikofaktoren: arterielle Hypertonie / Diabetes mellitus / Hypercholesterinämie / Nikotinabusus / positive Thrombophiliemarker

**Hochrisiko-Patienten:** Alter > 60 Jahre / thromboembolische bzw. schwere Blutungskomplikationen / Thrombozytenzahl > 1.500.000 pro µl

**American Journal of Hematology: Primary Myelofibrosis (2012 update)**

A. Tefferi, Primary myelofibrosis: 2012 update on diagnosis, risk stratification, and management, American Journal of Hematology 86:1018-1026, 2011




High, intermediate-2, intermediate-1, and low risk categories areaccording to the DIPSS-plus:

**DIPSS**(Dynamic International Prognostic Scoring System)**-plus** 8 risk factors for inferior survival:

- Age >65 years
- Hemoglobin <10 g/dL
- Leukocyte count >25 x $10^9$/L
- Circulating blasts ≥ 1%
- Presence of constitutional symptoms
- Presence of unfavorable karyotype
- Platelet count < 100 x $10^9$/L
- Presence of red cell transfusion need

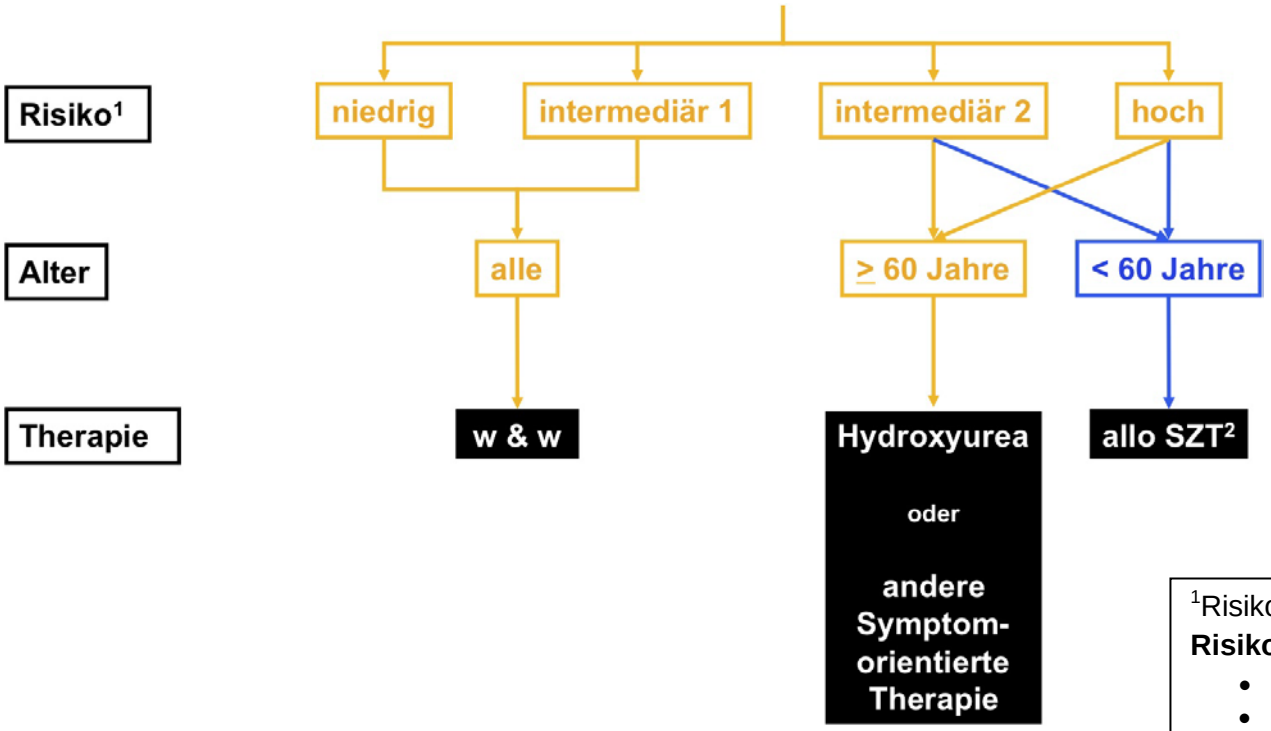
**Low Risk:** no risk factors
**Intermediate-1 Risk:** 1 risk factor
**Intermediate-2 Risk:** 2 or 3 risk factors
**High Risk:** ≥ 4 risk factors

Please note that a transfusion-dependent patient automatically has two risk factors because of transfusion need (one risk point) and hemoglobin < 10 g/dL (one risk point).

Very high risk group includes patients with monosomal karyotype, inv(3)/i(17q) abnormalities, or any two of circulating blasts > 9%, leukocytes ≥ 40 x $10^9$/L or other unfavorable karyotype

alloSCT = allogeneic stem-cell transplantation

**Primäre Myelofibrose**




[1]Risiko-Klassifikation:

**Risiko-Faktoren:**

- Alter > 65 Jahre
- Konstitutionelle Symptome (Fieber, Gewichtsverlust
- Hb < 10 g/dL
- Leukozyten > 25000/µl
- Blasten im PB =1%

**Niedrigrisiko: k**ein o.g. Kriterium liegt vor
**Intermedärrisiko 1:** ein o.g. Kriterium liegt vor
**Intermedärrisiko 2:** zwei o.g. Kriterien liegen vor
**Hochrisiko:** drei o.g. Kriterien liegen vor

[2]allo SZT = allogene Stammzelltransplantation

## Detaillierte Darstellung der Recherchestrategie:

**Cochrane Library am 22.01.2014**

| # | **Suchfrage: Spengalomalie/ Myelofibrose** |
|---|---|
| 1 | MeSH descriptor: [Primary Myelofibrosis] explode all trees |
| 2 | MeSH descriptor: [Splenomegaly] explode all trees |
| 3 | "myelofibroses":ti,ab,kw or "myelofibrosis":ti,ab,kw or "myeloproliferative":ti,ab,kw or splenomegal*:ti,ab,kw |
| 4 | myeloid*:ti,ab,kw and metaplasi*:ti,ab,kw |
| 5 | osteomyelofibros*:ti,ab,kw |
| 6 | "bone marrow fibrosis":ti,ab,kw or "bone marrow fibroses":ti,ab,kw |
| 7 | myeloscleros*:ti,ab,kw or nonleukemic myelos*:ti,ab,kw |
| 8 | #1 or #2 or #3 or #4or #5 or #6 |
| 9 | #8 from 2009 to 2014 |

| # | **Suchfrage: Polycythemia Vera** |
|---|---|
| 1 | MeSH descriptor: [Polycythemia Vera] explode all trees |
| 2 | MeSH descriptor: [Thrombocythemia, Essential] explode all trees |
| 3 | polycythemia* or polycythaemia*:ti,ab,kw and vera or rubra or ruba:ti,ab,kw |
| 4 | erythremia*:ti,ab,kw |
| 5 | osler* or vaquez*:ti,ab,kw and "disease":ti,ab,kw |
| 6 | thrombocythemia or thrombocythaemiaor or thrombocytosis:ti,ab,kw |
| 7 | #1 or #2 or #3 or #4 or #5 or #6 |
| 8 | #7 from 2009 to 2014 |

**SR, HTAs in PubMed (Medline) am 22.01.2014**

| # | **Suchfrage: Spengalomalie/ Myelofibrose** |
|---|---|
| 1 | "Primary Myelofibrosis"[Mesh] |
| 2 | Splenomegaly[Mesh] |
| 3 | myelofibros*[Title/Abstract] OR “MPF”[Title/Abstract] |
| 4 | myeloproliferativ*[Title/Abstract] OR “MPN”[Title/Abstract] OR “MPS”[Title/Abstract] OR “MPD”[Title/Abstract] OR “CMPD”[Title/Abstract] |
| 5 | splenomegal*[Title/Abstract] |
| 6 | myeloid*[Title/Abstract] AND metaplasi*[Title/Abstract] |
| 7 | osteomyelofibros*[Title/Abstract] OR osteofibrosi*[Title/Abstract] |
| 8 | (“bone marrow fibrosis”[Title/Abstract]) OR “bone marrow fibroses”[Title/Abstract] |
| 9 | myeloscleros*[Title/Abstract] OR nonleukemic myelos*[Title/Abstract] |
| 10 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 |
| 11 | (#10) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) |
| 12 | (#10) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR |

| | |
|---|---|
| | Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))) |
| 13 | #11 OR #12 |
| 14 | (#13) AND ("2009/01/01"[PDAT] : "2014/01/22"[PDAT]) |

| # | **Suchfrage Polycythemia Vera** |
|---|---|
| 1 | (Polycythemia Vera[MeSH Terms]) OR "Thrombocythemia, Essential"[Mesh] |
| 2 | (polycythemia*[Title/Abstract] OR polycythaemia*[Title/Abstract]) AND (vera[Title/Abstract] OR rubra[Title/Abstract]) |
| 3 | erythremia*[Title/Abstract] |
| 4 | (osler*[Title/Abstract] OR vaquez*[Title/Abstract]) AND disease[Title/Abstract] |
| 5 | thrombocythemia*[Title/Abstract] OR thrombocythaemia*[Title/Abstract] OR thrombocytosis[Title/Abstract] |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 |
| 7 | (#6) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) |
| 8 | (#6) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))) |
| 9 | #7 OR #8 |
| 10 | (#9) AND ("2009/01/01"[PDAT] : "2014/01/22"[PDAT]) |

**Leitlinien in PubMed (Medline) am 22.01.2014**

| # | **Suchfrage: Spengalomalie/ Myelofibrose** |
|---|---|
| 1 | "Primary Myelofibrosis"[Mesh] |
| 2 | Splenomegaly[Mesh] |
| 3 | myelofibros*[Title/Abstract] OR “MPF”[Title/Abstract] |
| 4 | myeloproliferativ*[Title/Abstract] OR “MPN”[Title/Abstract] OR “MPS”[Title/Abstract] OR “MPD”[Title/Abstract] OR “CMPD”[Title/Abstract] |
| 5 | splenomegal*[Title/Abstract] |
| 6 | myeloid*[Title/Abstract] AND metaplasi*[Title/Abstract] |
| 7 | osteomyelofibros*[Title/Abstract] OR osteofibrosi*[Title/Abstract] |

| | |
|---|---|
| 8 | (“bone marrow fibrosis”[Title/Abstract]) OR “bone marrow fibroses”[Title/Abstract] |
| 9 | myeloscleros*[Title/Abstract] OR nonleukemic myelos*[Title/Abstract] |
| 10 | #1 OR #2 OR #3 OR #5 OR #4 OR #6 OR #7 OR #8 OR #9 |
| 15 | (#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR consensus[Title]) |
| 16 | (#15) AND ("2009/01/01"[PDAT] : "2014/01/22"[PDAT]) |

| # | **Suchfrage: Polycythemia Vera** |
|---|---|
| 1 | (Polycythemia Vera[MeSH Terms]) OR "Thrombocythemia, Essential"[Mesh] |
| 2 | (polycythemia*[Title/Abstract] OR polycythaemia*[Title/Abstract]) AND (vera[Title/Abstract] OR rubra[Title/Abstract]) |
| 3 | erythremia*[Title/Abstract] |
| 4 | (osler*[Title/Abstract] OR vaquez*[Title/Abstract]) AND disease[Title/Abstract] |
| 5 | thrombocythemia*[Title/Abstract] OR thrombocythaemia*[Title/Abstract] OR thrombocytosis[Title/Abstract] |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 |
| 11 | (#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR consensus[Title]) |
| 12 | (#11) AND ("2009/01/01"[PDAT] : "2014/01/22"[PDAT]) |

**Literatur:**


1. **Ahmed W, Van Etten RA**. Signal transduction in the chronic leukemias: implications for targeted therapies. Curr Hematol Malig Rep 2013; 8 (1): 71-80.
2. **Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Hehlmann R, Hoffman R, Kiladjian JJ, Kroger N, Mesa R, McMullin MF, Pardanani A, Passamonti F, Vannucchi AM, Reiter A, Silver RT, Verstovsek S, Tefferi A**. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol 2011; 29 (6): 761-70.
3. **Cacciola RR, Di FE, Pezzella F, Tibullo D, Giustolisi R, Cacciola E**. Effect of anagrelide on platelet coagulant function in patients with essential thrombocythemia. Acta Haematol 2007; 118 (4): 215-8.
4. **Griesshammer M., Petrides PE, Lengfelder E**. Primäre Myelofibrose (PMF). Stand: März 2010. Berlin (Ger): Deutsche Gesellschaft für Hämatologie und medizinische Onkologie e V (DGHO) 2010; http://www.dgho-onkopedia.de/onkopedia/leitlinien/primaere-myelofibrose-pmf , Zugriff am 23.01.2014.
5. **Gu L, Su L, Chen Q, Xie J, Wu G, Yan Y, Liang B, Tan J, Tang N**. Ruxolitinib for myelofibrosis (Provisional abstract). Database of Abstracts of Reviews of Effects 2013; (4): 927-31.
6. **Harrison CN, Campbell PJ, Buck G, Wheatley K, East CL, Bareford D, Wilkins BS, van der Walt JD, Reilly JT, Grigg AP, Revell P, Woodcock BE, Green AR**. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 2005; 353 (1): 33-45.
7. **Kiladjian JJ, Rain JD, Bernard JF, Briere J, Chomienne C, Fenaux P**. Long-term incidence of hematological evolution in three French prospective studies of hydroxyurea and pipobroman in polycythemia vera and essential thrombocythemia. [Review] [42 refs]. Seminars in Thrombosis & Hemostasis 2006; 32 (4 Pt 2): 417-21.
8. **Matthews JH, Smith CA, Herst J, Lee D, Imrie K, Hematology Disease Site Group**. The Management of Malignant Thrombocytosis in Philadelphia Chromosome-Negative Myeloproliferative Disease: Guideline Recommendations. Stand: Januar 2008. Toronto (ON): Cancer Care Ontario 2008; ([ARCHIVED2013 Nov]. Program inEvidence-based Care Evidence-Based Series No.:6-9 ARCHIVED 2013): https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34319 , Zugriff am 23.01.2014.
9. **National Cancer Institute**. Primary Myelofibrosis (PDQ®). Stand:11/2013. Bethesda, MD (US): National Cancer Institut 2013; http://www.cancer.gov/cancertopics/pdq/treatment/myeloproliferative/HealthProfessional/page4 , Zugriff am 23.01.2014.
10. **National Cancer Institute (NCI)**. Essential Thrombocythemia (PDQ®). Stand: Juli 2011. Bethesda, MD (US): National Cancer Institut 2011; http://www.cancer.gov/cancertopics/pdq/treatment/myeloproliferative/HealthProfessional/page4 , Zugriff am 23.01.2014.
11. **Nordic MPD Study Group**. Guidelines for the diagnosis and treatment of patients with polycythemia vera, essential thrombocythemia and primary myelofibrosis. Stand: März 2008. (NOR) Den norske legeforening 2008; nicht mehr verfügbar! http://www.legeforeningen.no/asset/38584/1/38584_1.pdf, letzter Zugriff am 16.01.2012.

12. **Petrides PE, Griesshammer M., Lengfelder E**. Essentielle (oder primäre) Thrombozythämie (ET). Stand: April 2010. Berlin (Ger): Deutsche Gesellschaft für Hämatologie und medizinische Onkologie e V (DGHO) 2010; http://www.dgho-onkopedia.de/onkopedia/leitlinien/essentielle-oder-primaere-thrombozythaemie-et , Zugriff am 23.01.2014.
13. **Reilly JT, McMullin MF, Beer PA, Butt N, Conneally E, Duncombe A, Green AR, Michaeel NG, Gilleece MH, Hall GW, Knapper S, Mead A, Mesa RA, Sekhar M, Wilkins B, Harrison CN**. Guideline for the diagnosis and management of myelofibrosis. Br J Haematol 2012; 158 (4): 453-71.
14. **Squizzato A, Romualdi E, Middeldorp S**. Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia 40. Cochrane Database Syst Rev 2008; (2): CD006503.
15. **Squizzato A, Romualdi E, Passamonti F, Middeldorp S**. Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. Cochrane Database of Systematic Reviews 2013; (4):
16. **Taylor SM, Molyneux ME, Simel DL, Meshnick SR, Juliano JJ**. Does this patient have malaria? JAMA 2010; 304 (18): 2048-56.
17. **Trelinski J, Tybura M, molewski P, obak T, hojnowski K**. The influence of low-dose aspirin and hydroxyurea on platelet-leukocyte interactions in patients with essential thrombocythemia. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 2009; 20 (8): 646-51.