Polycythemia Vera

Treatment Policy Prepared by
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Introduction

PV is a chronic, clonal, myeloproliferative disorder, classically associated with an increase in red cell mass, leukocytosis, thrombocytosis, splenomegaly, thrombosis and bleeding.

2 in 100 000 incidence with peak age of 60.

20% of patients present with thrombosis and 30% develop in follow-up despite control of disease in a long-term follow-up study of 1213 patients over a 20-year period, followed for a median of 6 years [1].

- Thrombosis sites – stroke/TIA > AMI > DVT/PE > Peripheral arterial thrombosis > hepatic /portal vein thrombosis
  - Risk 3%/yr, 60% arterial
  - Patients < 60 years AND no history of prior thrombosis – 20%/15 years (1%/yr)
  - Patients > 60 years OR history of thrombosis – 40%/15 years (3%/yr)

- Cause of death: 50% related to PV (24% arterial thrombosis, 15% AML, 5% venous thrombosis, 3% major hemorrhage, 2% spent phase complications)

- Highest rates of thrombosis = age > 70, history of thrombosis, active disease (> 6 phlebotomies/yr) [2]

- Hepatic and portal vein thrombosis can be the first manifestation of the disease before rise in red blood cell mass or platelet count [3]

- 5% of patients with ET eventually fulfill the criteria for PV [4]

Symptoms

(a) Hyperviscosity – headache, dizziness, tinnitus, dyspnea, weakness, chest pain
(b) Ruddy skin
(c) Hemorrhage
(d) Splenomegaly – 66%
(e) Cyanotic extremities
(f) Aquagenic pruritus
(g) Erythromelalgia (esp. with extreme thrombocytosis)
(h) Arterial & Venous thrombosis
(i) Hypertension
(j) Gastric and duodenal erosions and ulcers

- Median survival of untreated PV is 18 months

- 15% will progress to myelofibrosis at 10 years, with median life-expectancy after the diagnosis of the spent phase was 4.4 yrs (0.5 to 9 years)
Definitions [5]

The following criteria are used to make diagnosis of PV:

A Criteria

1. Raised RBC mass (male > 36 ml/kg: females > 32 ml/kg)
2. Absence of any secondary cause of erythrocytosis
3. Bone marrow biopsy – increased cellularity, enlarged megakaryocytes with hyperploid nuclei or clusters of megakaryocytes, increase reticulin (optional)

B Criteria

1. Platelet count > 400
2. Granulocytes > 10
3. Splenomegaly by palpation or ultrasound
4. Spontaneous EEC in absence of epo

A123 – early PV
A123 + any B – overt PV
A3 + B1 – Essential thrombocythemia

Baseline Investigations

- CBC and blood film
- Ferritin
- Creatinine
- Peripheral blood or BM for PCR for BCR-ABL to exclude CML
- Oxygen saturation
- RBC mass
- Ultrasound abdomen – if spleen not palpable
- BM – Confirmatory marrow histology should be established before embarking on cytoreductive therapy.
  - BM shows hyperplasia of the myeloid, erythroid and megakaryocyte lineages, enlarged megakaryocytes with hyperploid nuclei or clusters of megakaryocytes, increase reticulin
  - Cytogenetics – 30% have a detectable clonal abnormality; del 20q is the most common

Management (Chemotherapy)

Treatment Objectives

1. Longest survival
2. Fewest complications of disease – thrombosis, bleeding, and myelofibrosis (MF)
3. Fewest complications of treatment – AML, MDS, NHL, other malignancies

Goal – HCT > 0.45
Hazardous to aggressively phlebotomize at diagnosis – therefore isovolemic therapy for extreme erythrocytosis (Hct > 0.60) at diagnosis

Important Studies

1. PVSG-01 RCT – phlebotomy vs. 32-P vs. chlorambucil [6]
   - Patients in the phlebotomy alone arm had an unacceptable risk of thrombosis vs. patients on 32-P or chlorambucil had higher rates of AML, NHL, and carcinomas of the GI tract & skin; no differences in the myelofibrosis rates between the three arms.
   - 30% of all deaths were due to thrombosis; 1/3 of all thrombotic events were fatal
A subsequent publication regarding this cohort was published in 1994 [7]

- Chlorambucil – 22/42 died due to malignancies
- P32 – 60 patients; @ 15 years 78% alive @ 20 years 55% alive (risk of MF 19% at 15 yrs, 53% at 20 yrs)
- Phlebotomy – 56 patients; only 37/56 still on phlebotomy alone at 3 yrs due to intolerance/thrombosis/thrombocytosis; at 9 yrs only 7/56 on phlebotomy alone (6 of 7 have MF)

2. PVSG-05 RCT – phlebotomy + 900 mg/d ASA + persantine 225 mg/d vs. 32-P – addition of antithrombotic agents failed to protect patients from thrombosis and increased the rate of life-threatening hemorrhage (20% vs. 5% at 2 yrs) [8]

3. PVSG-08 Cohort Study [9] – 51 patients with PV treated with hydroxyurea; in 80% Hct was controlled by 12 weeks and 88% control of thrombocytosis by 12 weeks, followed for 12 years (range 9-15 yrs), average dose 500-1000 mg/d

- PVSG-08 compared to PVSG-01 (phlebotomy arm) – patients in the PVSG-08 cohort had a higher rate of previous thrombosis (35% vs. 14%); reduced thrombosis rate in HU group with 8 years of f/u from 38% to 13%; trend toward an increased AML/MDS rate in HU arm (5.9% vs. 1.5%)

4. Interferon Studies (three published studies):

- 54 patients treated with IFN mIU/d until response then 2.5 mIU/d – at 4 yrs, 72% maintained response even after drug stopped (median follow-up 39 weeks); 13% had to stop due to adverse effects [10]
- 38 patients with PV 9 mIU/wk – 30% CR; 25% flu like symptoms, 13% had to stop due to late (weakness) toxicity [11]
- 32 patients with PV – 12 mU/wk x 1 yr, 9 mU/wk x 1 yr, then 12 mU/wk thereafter – reduced thrombosis (1.8%/yr vs. 3.6% before treatment); reduced frequency of phlebotomy (0.49/month to 0.19/month) [12]

5. Patients age > 65 [13] – study by the French PSG randomized patients to HU (10 mg/kg/d) or no HU after clinical remission induced by P-32 in 461 patients

- OAS – trend toward a reduction in those patients on HU (9.1 vs. 11.2 years) vs. 11.4 for age matched controls
- No difference in thrombosis rate (25% at 10 years)
- Greater risk of MDS/AML after 10 years in the HU arm (21% vs. 14%)
- No reduction in myelofibrosis – 30% at 15 years

6. Patients age < 65 [14] – n = 292 patients, randomized to HU (25 mg/kg then 10 mg/kg) vs. pipobroman (1.2 mg/kg then 0.5 mg/kg)

- No difference in thrombosis rate (15% at 10 yrs), AML rate 20% at 15 yrs, or survival
- Better hematologic control with pipobroman and less MF with pipobroman (40 vs. 17% at 15 years)
- Higher mortality than age matched controls
- Drug not available in Canada or USA

7. Anagrelide [15] – n = 113 patients with PV; 70% response rate (plt < 600); average dose 2.4 mg/d; time to response 20 days; adverse: headache 25%, palpitations 15%, diarrhea 25%, fluid retention 15%, intolerance rate 13%; rate of bleeding/thrombocytopenia was 9/942 patients (1%)

- Insufficient data on the impact of anagrelide on thrombosis rate in PV
# TSRCC Policy

<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical Manifestations</th>
<th>Management</th>
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<tbody>
<tr>
<td>&lt; 70 YRS</td>
<td>Asymptomatic</td>
<td>Phlebotomy alone</td>
</tr>
<tr>
<td></td>
<td>Thrombosis</td>
<td>Interferon (alternatively hydroxyurea) + Phlebotomy</td>
</tr>
<tr>
<td></td>
<td>Symptomatic Splenomegaly</td>
<td></td>
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<tr>
<td></td>
<td>Disabling symptoms</td>
<td></td>
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<tr>
<td>≥ 70 yrs</td>
<td>All patients</td>
<td>Hydroxyurea + Phlebotomy</td>
</tr>
</tbody>
</table>

## Dosage

1. Hydroxyurea 15 mg/kg starting dose; increase by 5 mg/kg q6 wks as needed to maintain hematocrit < 0.45 and platelet count < 600
2. Interferon 3 mU sc qMWF; commence at 1 mU sc qMWF and titrate up to 3 mU sc qMWF over 1 month; increase dose if required q8wks; maximum dose 5 mU/M2/d
3. Phlebotomy – start qwk until Hct < 0.45; then as needed
4. Anagrelide 0.5 mg po qid; can titrate up to a maximum of 1.0 mg po qid; (Patients with renal and hepatic dysfunction should be closely monitored during the start of therapy)

## Perioperative Management

- Patients should have good hematologic control of disease, if possible, for 6 weeks preop
- Bleeding time is not accurate in identifying patient at risk of perioperative bleeding [16]
- Preop ensure DIC work-up is negative (D-Dimers/Fibrinogen) – patients with evidence of DIC have a higher incidence of perioperative bleeding. If possible surgery should be delayed until evidence of DIC resolves. DIC may be responsive to hydroxyurea.

## Anticoagulants/Antiplatelet Agents

- GISP Trial – Low dose ASA has been shown to be safe at 40 mg/d in safety trial of 112 patients compared to placebo; no difference in thrombosis rate at 1 year follow-up [17]
- Efficacy of low dose ASA un-proven – ongoing European ECLAP trial (dose 40 mg/d)
- High dose ASA – see PVSG-05 above, not useful

### Recommendation:

- Venous thrombosis – warfarin for 3 months minimum, may consider stopping warfarin once Hct controlled; consider hypercoagulable assessment
- Arterial thrombosis or ischemic heart disease – ASA 40-80 mg/d; rule out other causes of stroke (perform dopplers or echocardiogram as needed)

## Management of the Spent Phase

- **TRANSFUSIONS** – no manipulation of cellular products required (i.e. irradiation or CMV-negative products)
- **Splenomegaly** – therapeutic options include – IFN, Hydroxyurea; splenectomy may result in an increased risk of AL transformation (Although not confirmed by all investigators); splenic irradiation (200-300 cGy in 10-15 daily fractions) usually results in only temporary benefit (3-6 months) and may preclude future splenectomy due to scarring
- **Extramedullary Hematopoiesis** (spinal cord, peritoneal or pleural cavities) – radiation therapy
## Outcome Data

(Managed with phlebotomy and/or hydrea; estimates based on all the reported studies referred below)

<table>
<thead>
<tr>
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<th>5 yrs (%)</th>
<th>10 yrs (%)</th>
<th>15 yrs (%)</th>
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<tbody>
<tr>
<td>Death</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>10</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>5</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>1</td>
<td>1-3</td>
<td>5-10</td>
</tr>
<tr>
<td>AML with HU tx</td>
<td>1</td>
<td>5</td>
<td>15-20</td>
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## Monitoring

- Hydroxyurea – q2wkly blood counts x 8 weeks then q8 weeks
- Interferon – q2 wkly blood counts x 8 weeks then q8 weeks
- Anagrelide – q2wks blood counts x 6 weeks then q8 weeks
- Phlebotomy alone – hematocrit q8 weeks

## References