Today's Treatment

Blood and Neoplastic Diseases

Thrombocytopenia

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British Medical Journal, 1974, 2, 324-325

There are many causes of thrombocytopenia, but they can be broadly divided into two groups: firstly, decreased platelet production; and, secondly, increased platelet destruction or utilization. In most cases one or other of these mechanisms will be responsible; in some both may be operative. The prognosis and correct treatment of thrombocytopenia depend on the cause, and thus a precise aetiological diagnosis is of paramount importance. In many instances thrombocytopenia is just one of several haematological abnormalities resulting from disease affecting the bone marrow or other organs.

The clinical importance of thrombocytopenia is related to the bleeding hazard, but this is very variable and often not closely correlated with the platelet count. At one end of the spectrum are those patients with platelet counts as low as 30,000/ μ l, and sometimes lower, who have little or no bleeding or purpura and who often require no specific treatment. At the other end are those with widespread purpura and frank bleeding in whom the platelet count has fallen below 10,000/ μ l; these patients require active treatment.

It cannot be too strongly emphasized that a low platelet count is not in itself sufficient reason for active treatment. The thrombocytopenia must be assessed in the broad clinical context, taking into account the extent of the purpuric or bleeding manifestations, the nature of the underlying or preceding disease, the drugs the patient has received or is receiving, the need for surgery or whether surgery has just been performed, and the presence of other haemostatic abnormalities. As in other disorders, in treating haematological disease a useful precept is "don't just treat the blood or platelet count, treat the patient."

Therapy

The choice of therapy depends on the cause of the thrombocytopenia. In aplastic anaemia, acute leukaemia, myelomatosis, myelofibrosis, or metastases involving the bone marrow widely thrombocytopenia is due to a failure of platelet production. In aplastic anaemia the object is to stimulate haemopoietic recovery, including thrombopoiesis, by using corticosteroids. In acute leukaemia therapy is directed at getting rid of the leukaemic cells with appropriate cytotoxic drugs, anti-metabolites, and immunotherapy (dealt with in a later article in this series)—the approach to metastatic disease being similar with additionally the use of appropriate hormonal and radiation therapy. The cytotoxic drug vincristine has a thrombopoietic effect.¹

When platelets are destroyed at an increased rate, as in autoimmune or drug-induced thrombocytopenia, or when there is increased consumption of platelets (as in disseminated intravascular coagulation) therapy is aimed at slowing down or stopping their excessive destruction or consumption.

Platelet transfusions² are sometimes used, particularly in the conditions due to failure of platelet production.

Intramuscular injections should if possible be avoided in patients with severe thrombocytopenia because of the risk of large and painful haematomata at the injection site, and drugs should preferably be given orally or intravenously, care being taken to apply appropriate pressure to venepuncture sites to prevent leakage of blood.

It is not possible to discuss here the detailed management of all the thrombocytopenic and purpuric states which may be encountered. Guidelines to the treatment of some of these disorders are briefly described below.

Thrombocytopenia due to Decreased Platelet Production

APLASTIC ANAEMIA

Thrombocytopenia is always present in aplastic anaemia and those patients with platelet counts below 20,000/ μ l are liable to develop serious bleeding. Because they may have a serious reduction in the number of neutrophil polymorphs they are also prone to severe infections—which in turn exacerbate the thrombocytopenia and thus the bleeding tendency. In those patients in whom the bone marrow function recovers, the platelets are usually the last of the blood cells to return to normal; furthermore, the recovery may take years so that recurrent bleeding episodes may continue for a long time.

At the start of treatment all drugs which the patient will have been treated with should, if possible, be withdrawn. Anabolic steroids are of value in stimulating erythropoiesis but have no effect on thrombopoiesis. Corticosteroids, such as prednisolone, may ameliorate bleeding episodes or prevent their recurrence by stimulating platelet production, but even though the platelet count does not rise, the patient's condition may improve perhaps owing to an effect of the steroids on vascular function.

Prednisolone in a daily dose of 0.75 mg/kg is worth a trial for three weeks, when the dose should be reduced over a week and then stopped, whether or not the platelet count has risen. A short course may tide the patient over a serious haemorrhagic phase. The use of steroids should be confined to serious bleeding episodes. Their long-term use in a chronic disease is potentially dangerous in that it predisposes to severe infections, to which these patients are in any case particularly prone because of the accompanying severe neutropenia. If steroids produce a rise in the platelet count to 20,000/ μ l or more, or a rise in the neutrophil count to 200/ μ l

or more, and if the maintenance of this improvement depends on continuation of steroid therapy then the lowest effective dose should be used, preferably not exceeding 10 mg/day. Nevertheless, every effort should be made to stop the steroids as soon as possible, despite persistent thrombocytopenia, provided that this is not followed by troublesome bleeding.

Serious bleeding in patients with aplastic anaemia is frequently precipitated by intercurrent infections, viral or bacterial. These patients are prone to septicaemias and blood cultures should, if possible, be taken and then antibiotic treatment started, a suitable combination covering a wide range of bacteria being gentamicin, ampicillin, and clindamycin given intravenously in recommended doses. Infections can suppress bone marrow function especially if this is already severely compromised as in aplastic anaemia. Successful control of the infection will promote haemopoietic recovery.

Platelet Transfusions

Platelet transfusions are used only for controlling serious bleeding, such as massive gastrointestinal or suspected intracranial haemorrhage, and then for just long enough to tide the patient over the acute episode. These patients will usually be anaemic as well and fresh whole blood will supply red cells and viable platelets. This may be supplemented with platelet concentrates from 6 to 12 units of blood, depending on the size of the patient, given daily, if the bleeding is not being controlled with fresh whole blood alone. The number of platelets that can be provided in whole blood is limited by the problem of hypervolaemia, and to raise the platelet count substantially platelet concentrates must be used.

Platelet transfusions should be limited to short-term use. It is both unnecessary and undesirable to give platelets to patients with low platelet counts who are not having troublesome bleeding. The formation of antibodies to platelets is stimulated by repeated transfusion and renders subsequent platelet transfusions increasingly less effective. Furthermore, platelets cannot usually be obtained as readily as whole blood and they should be used with circumspection.

Other Measures

For control of menorrhagia progesterone preparations in appropriate dose are effective. For tooth extractions scrupulous care in extraction, careful packing of the socket with an absorbable dressing, oral epsilonaminocaproic acid (EACA), 5 g thrice daily for seven days, and oral penicillin for five days will help haemostasis, as in haemophilia. For major surgery platelet transfusions will be necessary and this can be supplemented with EACA given intravenously and then by mouth.

Acute Leukaemia

Severe thrombocytopenia—for example, platelet counts of less than 20,000/ μ l—is common in acute leukaemia and is often intensified during the induction phase of chemotherapy, particularly in the acute myeloblastic form. Serious haemorrhage, an ever-present hazard, may be prevented or controlled in the short term with platelet transfusions. But it should be emphasized that the recovery of thrombopoiesis depends on the induction of remission.

Platelet transfusions are used for relatively brief periods of one to three weeks to tide the patient over the critical period when attempts are being made to achieve a remission with appropriate chemotherapy. Some patients, particularly children with acute lymphoblastic leukaemia, start going into remission quickly, the period of severe thrombocytopenia thus being relatively short, and they require few or no platelet transfusions. In many patients, especially adults, the period of

remission induction with severe thrombocytopenia is prolonged for several weeks and they may die from haemorrhage before remission sets in. These patients should receive platelet transfusions. For adults platelet concentrates from 6 units of blood are recommended on alternative days until the platelet count has risen to 20,000/ μ l or more. They will also need red cells for their anaemia and thus appropriate amounts of fresh whole blood are used as well.

As in patients with aplastic anaemia, septicaemias exacerbate the bleeding tendency and must be treated appropriately at the same time. In these patients the daily platelet requirement is even greater and platelet concentrates from up to 12 units of blood may be required daily to achieve a satisfactory haemostatic response. The requirement is particularly great in patients with acute promyelocytic leukaemia which may be complicated by disseminated intravascular coagulation. The demand for platelet concentrates for patients with acute leukaemia imposes a tremendous strain on the limited resources of the Blood Transfusion Service and platelets may not always be available when required and in the necessary amounts. Fresh blood can be haemostatically effective within limits and platelet concentrates from even a few units of blood will help haemostasis.

Vincristine, a drug used for its antieoplastic activity, especially in acute lymphoblastic leukaemia, has the additional virtue of stimulating thrombopoiesis.

Other Marrow Replacement Diseases

The management of thrombocytopenia in myelomatosis, lymphosarcoma, and other myeloproliferative diseases is similar to that described for acute leukaemia. In myelofibrosis, the management resembles that outlined for aplastic anaemia, with the addition of a daily oral dose of 5 mg folic acid.

Extensive infiltration of the bone marrow with malignant metastases may give rise to severe thrombocytopenia and this will improve with effective anti-tumour treatment as in carcinoma of the breast or prostate. In carcinomatosis of the breast, adrenalectomy or hypophysectomy may be indicated but in severely thrombocytopenic patients there is a risk of dangerous surgical haemorrhage. If the operation can be deferred for about two weeks, vincristine (2 mg intravenously once-weekly for two weeks), is worth a trial—a rise in the platelet count to levels above 50,000/ μ l may follow and surgery can then be undertaken with better haemostasis.³ Otherwise, platelet transfusions in the form of fresh whole blood and platelet concentrates will be needed to cover the operation and the early postoperative period, the platelets from 12 units of blood being given preoperatively and then daily from 6 units of blood for three days. An antifibrinolytic agent such as EACA, 5 g intravenously immediately preoperatively and then 5 g 8-hourly postoperatively by mouth, will help to maintain haemostasis.

Marrow Depression after Chemotherapy

Intensive chemotherapy for treatment of malignant disease or for immunosuppression may inadvertently produce bone marrow aplasia and thrombocytopenia severe enough to cause serious bleeding. These patients will need fresh whole blood and platelet transfusions to tide them over the period of severe marrow depression until haemopoiesis begins to recover, usually in one to two weeks after the offending drugs are stopped.

References

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