

CASE DISCUSSION: TO STEM CELL TRANSPLANT OR NOT?

CASE

JD is a 10.5 year old girl who has had rheumatoid factor negative, polyarticular JRA (JIA) since age 5 years. She has over 25 joints affected since the onset without resolution of her morning stiffness (1-2 hours) and fatigue. The joints affected include PIP's and MCP's, wrists, elbows, knees, ankles, and subtalar joints. Her hemoglobin has ranged from 9-10.5 gm%, her platelet count from 300,000 to 500,000, and her ESR from 55 mm/hr to 110 mm/hr.

She was initially begun on naproxen therapy (15 mg/kg), but weekly subcutaneous methotrexate (0.7 mg/kg, 17.5 mg/kg/week) was added after 3 months of naproxen due to minimal improvement on the NSAID. She was placed on an aggressive physical and occupational therapy program which continued throughout the treatment. She improved in the next 8 months with a decreased joint count and improved functioning. She had a major flare of her arthritis at 11 months after onset and the methotrexate dose was increased to 22.5 mg/week (1 mg/kg). She improved on this dose for the next 2 months and then stabilised with 10-15 active joints over the next 11 months. Weekly methylprednisolone pulses (30 mg/kg/dose) were added at 2 years after onset and the methotrexate switched to the intravenous route due to the lack of further improvement.

On the naproxen, methotrexate, and methylprednisolone treatment her symptoms improved but her joint count and severity as well as ESR

remained unchanged. At age 7.5 years, radiographs demonstrated diminished carpal spaces and knee joint spaces with juxtaarticular osteoporosis. Methylprednisolone was stopped after six months of therapy, the methotrexate was again given SQ., and prednisone was started at a dose of 5 mg per day.

At age 8 the child began missing 1-2 days of school per week. Joint injections of wrists, elbows, knees, and ankles were performed at age 8 1/2 with an excellent response initially but return to baseline 3 months later. At age 9 years, etanercept (0.4 mg/kg/dose) was added to the SQ. methotrexate and used for 1 year with only minimal improvement of decreased stiffness and pain. The dose was increased to (16 mg/m²) at age 10 with no response over the next 6 months. At age 10 1/2 years the child began complaining of severe left hip pain. Radiographs revealed mild narrowing of the hip joint. Despite the etanercept, methotrexate, naproxen, and prednisone therapy, she starting missing more school and had to stop all regular physical activity.

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In the described case all available conventional therapy has failed. Continuation of current ineffective therapy will certainly cause significant drug toxicity and induce a chronic immune suppressive state that renders a patient a risk for opportunistic infections such as *Pneumocystis Carinii* and tuberculosis. Furthermore the ongoing disease activity will induce widespread joint destruction and poor quality of life. Although this case discussion is about a child with a polyarticular JIA, a recent case of a child with severe systemic JIA at our center also illustrates the risks of aggressive

remissive therapy in any child with JIA. We observed in our clinic a similar patient with systemic onset JIA that developed a drug-associated lymphopenia and decreased in vitro responsiveness to mitogens, antigens and PPD. Due to lack of efficacy of conventional treatment her infliximab dose was increased from 5mg/kg to 20 mg/kg during 4 months. She did not improve and her spiking fever changed in pattern to more chronic. Her infliximab was discontinued. Within 4 months she developed a fatal tuberculosis, initially presenting as a cold skin abscess. Despite anti-tuberculosis treatment including isoniazid, ethambutol, rifampicin and pyrazinamid, she developed respiratory insufficiency and cardiac arrest due to widespread miliary tuberculosis in lungs and heart.

This example illustrates 2 points. First, it points painfully at the risk of adding more and more immunosuppression to poor risk patients. At several pediatric rheumatology meetings of the past 3 years it has been put forward that patients with SO-JIA are less responsive to TNF-a blockade¹. One should not automatically increase the dose in such cases, but realize its associated infectious risks too. Secondly it illustrates the importance of carefully screening patients before one might take a patient to transplant, even if this is autologous (and regarded as low risk). The limited available data on newer drugs such as leflunomide do not show a much more effective profile as compared to methotrexate. This child will most likely also be unresponsive to this drug.

The possibility of autologous stem cell transplantation should be considered here and the patient should be screened in a transplant Center for contra-indications such as persistent systemic activity, chronic infections,

cardio-respiratory toxicity^{2,3}. Especially the case fatalities observed in the first 2 years when the efficacy of SCT for drug resistant JIA was studied, clearly illustrate this³. After careful selection one could offer autologous SCT, given the observed prolonged (more than 2 years) drug free remissions in more than 50% of 34 children treated in 9 different European transplant centers.

With regard to the type of transplant, much controversy exists⁴. It seems from the data of the 34 European patients that potent immunosuppression as a preparative regimen is effective whether low dose total body irradiation is added or not³. The issue of autologous versus allogeneic transplantation is not resolved. Allogeneic transplantation certainly has a theoretical advantage of replacing the entire lymphocyte population, but is associated with increased risks such as infections and graft versus host disease. The observed remissions after autologous SCT may however still appear to be transient given the observed occurrence of disease (in 25% of cases, within 18 months) and the fact that it may take several years for T lymphocytes to repopulate after such a immune suppressive transplant regimen. All in all, the matter asks for ongoing and careful study in a number of experienced pediatric rheumatology centers. It is of importance international collaborations will produce a limited number of treatment protocols that can be studied in large multicenter trials. Recently, the European Marrow and Blood Transplant (EBMT) group, the working parties for autoimmune diseases and immunodeficiencies again strongly recommended uniform multicenter studies. We will put forward such a proposal soon.

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In approaching the treatment of the case presented to us for discussion, it is important to deal with the relevant treatment issues in order. This first issue to address is the cause of the severe left hip pain with a radiograph showing “only mild narrowing of the hip”. The critical question is to determine the cause of the pain and to not just assume it is secondary to the JRA. Important alternative etiologies to eliminate are avascular necrosis and infection. Her disease and treatment make either one a real possibility. Once both are eliminated, and if the imaging studies suggest inflammation is present in the hip, then this hip should be injected with corticosteroids to allow her to resume a more normal school and physical activity program.

This case presentation is an example of erosive, poly JRA of 4.5 years duration that has never been well controlled despite use of methotrexate in varying doses and routes of administration without stop for 4.25 years in combination with IV, oral and intraarticular steroids. In addition, after 4 years of active disease and the development of erosions seen at multiple sites on plain radiographs, etanercept was added in the approved dose without much benefit despite 12 months of treatment. After 12 months of etanercept at the standard dose, the etanercept dose was increased significantly for 6 more months without additional benefit.

Is it time to turn to stem cell transplant (SCT)? Most emphatically the answer is no! SCT is to be used only in those cases in which standard therapies have been used and failed. There are several effective treatment options left that all have significantly less risk for toxicity than SCT.

Unfortunately, what dictates treatment options for individual subjects in often times an issue of regulatory or financial constraints and not one based on clinical support or biologic plausibility. However, for this child, let us assume that clinical information will be the determinant and not regulatory or bureaucratic folly. Oh, the joys of cyber medicine!

First, although etanercept did not work, it is important to realize that tumor necrosis blocking agents are not all alike. There is some evidence that patients who fail to respond to one TNF blocker may respond to another. In 17 RA subjects who had failed to respond to etanercept (no clinical response in 5, partial or loss of response in 12), switching to infliximab at a standard dose resulted in significant clinical response in 16 of the 17 subjects. This was not a controlled or blinded study but does suggest that failure to respond to one of the TNF blockers does not preclude response to another 1. Infliximab at doses of 3-10 mg/kg per infusion given at 0, 2, 6 and then every 4-8 weeks has been used successfully in children with systemic² and polyarticular JRA³. An international double blind, placebo controlled trial of infliximab in children with polyarticular course JRA is currently in progress. Replacing etanercept with infliximab represents a viable option for this child. In our own clinic, we have several JRA subjects who failed to respond to etanercept who demonstrated excellent response to infliximab. There are no publications to address the response to etanercept in those who fail infliximab. Response to infliximab is generally quick and to minimize the time to evaluate the response to this therapy in this patient, I would use 10 mg/kg/dose and give infusions at 0, 2, 6 and then every 4 weeks for a maximum of 4-6 months on this therapy.

Interleukin 1 receptor antagonist (IL1 RA, Anakinra) has been shown to be efficacious in controlling both the clinical and radiologic manifestations of RA in adults in randomized, placebo controlled trials.⁴ Anakinra has been approved for clinical use by prescription in RA subjects in several countries including the United States. At this time, a randomized international trial is underway investigating the efficacy of anakinra in children with polyarticular JRA. This child would be an ideal candidate for such a trial. The demonstrated safety profile of anakinra in adults is clearly more reassuring than that of SCT and if enrollment in the JRA clinical trial is not an option, then treatment with prescription anakinra would be reasonable.

It is not only in the newest treatments that one should look for potential help for this child. Oral lower dose cyclosporine (2.5-5 mg/kg/day) has been shown to be efficacious in several controlled trials in adults with RA and open clinical observational experience in children with JRA has also shown benefit in some but not all subjects.

If the above therapies are unsuccessful, then cytotoxic therapies (azathioprine, cyclophosphamide and chlorambucil) are a possibility. However, information related to cytotoxic therapies in JRA is anecdotal, uncontrolled and their use introduces the concern for significant short and/or long-term complications. In my opinion, prior to initiation of cytotoxic therapy in this child, which in all likelihood would need to be continued for a long period to maintain any clinical benefit, she should be referred to and evaluated at a center that does SCT to see if the risk/benefit ratio would at that point weigh in favor of performing a SCT.

In conclusion, for this child there are several therapeutic options to try before considering SCT and hopefully, with the continued development of new treatments and the testing of those treatments in children, fewer and fewer children will need to be exposed to the risk of SCT.

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