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INTERFERON AND HEMATOPOIETIC GROWTH FACTORS THERAPY IN DECOMPENSATED CIRRHOSIS: SUGGESTED RECOMMENDATIONS

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ABSTRACT:

Decompensated cirrhosis has traditionally been considered a contraindication to interferon and ribavirin therapy. Whereas, the same may be true for advanced cirrhosis, which is only amenable to liver transplantation, there are reports in the literature in which antiviral therapy has been given in selected cases of early hepatic decompensation with reasonable results. Thus decompensation per se is no more an absolute contraindication to antiviral therapy. It, however, requires modifications in the dose regimen and close monitoring especially for the development of hematologic effects. In this article, the pros and cons of antiviral therapy in decompensated liver cirrhosis is given with special emphasis on how to avoid antiviral dose reductions/withdrawal secondary to the development of hematologic side effects by using hematopoietic growth factors (HGFs). At the end, suggested recommendations are given.

KEY WORDS: Chronic hepatitis C. Decompensated Cirrhosis. Antiviral Therapy. Hematopoietic Growth Factors.

INTRODUCTION:

Whereas, decompensated cirrhosis of liver has traditionally been considered a contraindication to antiviral therapy, the same is not true any more. Ribavirin-induced hemolytic anemia and interferon-induced neutropenia are one of the commonest causes of antiviral dose reductions/withdrawal, particularly in decompensated cirrhotics. Although, no consensus still exists, there are some recent reports in the literature that suggest the use of hematopoietic growth factors (HGFs) in selected cases of hemolytic anemia and neutropenia. Whereas, the addition of growth factors substantially increases the overall cost of the treatment, the same have provided an opportunity to institute antiviral therapy in some of the conditions previously included in the list of contraindications to antiviral therapy (like decompensated cirrhosis). Although more studies are needed to truly define the indications, dose regimen, side effects and therapeutic efficacy of these factors, the initial results are encouraging and hematopoietic growth factors appear to be a useful adjunct to the antiviral therapy.

DISCUSSION:

Chronic liver disease is said to be decompensated when one or the other complication of chronic liver disease has developed - ascites, variceal bleeding (secondary to portal hypertension), impaired hepatic synthetic function (hypoalbuminemia), and/or hepatic encephalopathy. Liver transplantation is the treatment of choice in all such cases. If Hepatitis C Virus (HCV) is not eradicated before going for liver transplantation, reinfection with HCV occurs in all transplant recipients *as a rule* and thus it is very common to see progressive posttransplantation disease of the allograft in such cases. Pre-transplantation HCV eradication is however associated with less likelihood of reinfection and this forms the rationale for treating decompensated cirrhotics waiting for transplantation with antiviral therapy[1].

Peginterferon-ribavirin combination therapy has limited efficacy in patients with decompensated cirrhosis[2;3]. Also, antiviral therapy is not safe from potentially serious adverse effects in this population group. As decompensated cirrhotics are more prone to develop hematologic side effects (neutropenia or thrombocytopenia) with antiviral therapy as compared to non-cirrhotics[4], patients who already have neutropenia or thrombocytopenia below the permissible limits (neutrophil count >1500/mm^3 & thrombocyte count >75,000/mm^3) are highly prone to develop life-threatening infections after starting antiviral therapy[5;6].

Also, decompensation may actually worsen with antiviral therapy as is the case with decompensated chronic hepatitis B cases[7]. Therefore, antiviral therapy, on one hand, should be initiated in low doses in patients with decompensated liver disease, and on the other hand, warrants more vigilant and close monitoring for side effects, especially hematologic.

The minimum effective doses of pegylated interferon and ribavirin appear to be 1 ìg/kg/week and 10.6 mg/kg/day respectively. In case a hematologic side effect develops, it is recommended to first reduce the dose to the minimum effective. If no or little improvement occurs in blood counts, use of hematopoietic growth factors (HGFs) should be considered. HGFs – erythropoietin (EPO)[8;9] for ribavirin-induced hemolytic anemia, and granulocyte colony-stimulating-factor (G-CSF)/granulocyte monocyte-colony stimulating-factor (GM-CSF)[10;11] for interferon-induced leukopenia may be used with an aim to avoid dose reductions, something that compromises drug efficacy and possibly SVR rates.

Possible indications of EPO include a fall in Hb level by >4g/dL, Hb levels of <11g/dL, and patients developing symptoms and signs of anemia (palpitations, dyspnea, easy fatigability, pallor)[12].

A suggested dose regimen for EPO is 20,000-40,000IU SQ weekly in three divided doses (max. 60,000IU/week) with an aim to maintain HB level of >11g/dL (return to the pretreatment level is not the aim)[13]. Another study suggested starting EPO therapy at a lower dose of 4,000IU SQ thrice weekly (12,000IU/week) and then increasing the dose depending upon the response[14]. The first evidence of a response to the thrice weekly EPO administration is an increase in the reticulocyte count within 10 days[15]. Since erythroid progenitors take several days to mature, a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients[16]. If the rate of rise of hemoglobin is greater than 1 g/dL over 2 weeks, it generally warrants decreasing EPO dose. This is because a greater than 1 g/dL rise in *any* 2 weeks during the course of the therapy has been associated with an increased risk of thromboembolic phenomenon, predisposing to myocardial infarction, stoke and even death[17]. Also, according to manufacturer's recommendations, a Hb level of greater than 12g/dL should not be aimed, the reason being potentially increased risk of thromboembolic phenomenon[18]. Once adequate HB level (=10g/dL) is achieved, ribavirin dose can be increased to the optimum level. Once started, adjunct EPO therapy may be required till the end of the treatment. In one study[19], the median duration of EPO treatment was 24 weeks (range 6–39).

Regarding G-CSF, the current recommendation is to reduce IFN dose if neutrophil count falls to $<0.5x10^9$/L, and discontinue it if it falls to $<0.3x10^9$/L[13]. Regarding platelet count, IFN dose should be reduced if platelet count falls to $<30x10^9$/L, and discontinued if it falls to $<20x10^9$/L[13]. The minimum effective dose of pegylated interferon appears to be 1 ìg/kg/week. If despite of reducing the pegylated interferon dose to the minimum effective level, neutrophil counts of $<0.5x10^9$/L and platelet counts of $<30x10^9$/L persist, instituting G-CSF therapy may be considered.

A suggested dose regimen is starting G-CSF therapy at a dose of 30MU SQ once weekly and then adjusting the dose as per the response/requirement. Complete blood counts should be asked twice or thrice weekly and response to therapy judged. Once adequate neutrophil count is achieved, IFN dose can be increased to the optimum level. Once started, adjunct G-CSF therapy may be required till the end of the treatment. In one study[20], the median duration of G-CSF therapy was 20 weeks (range 9–45).

CONCLUSION:

Decompensated cirrhosis of liver is no more an absolute contraindication to interferon therapy, although it warrants low-dose antiviral therapy and close monitoring of the patients especially for hematologic side effects. HGFs, though not routinely recommended, appear to be a useful adjunct to antiviral therapy to reduce antiviral dose reductions/withdrawal. Since, addition of HGFs substantially increases the overall cost of the therapy, more studies are needed to establish the lower cut off limits for different blood counts *applicable to our population* below which HGF therapy may be considered.

SUGGESTED RECOMMENDATIONS FOR INTERFERON THERAPY IN DECOMPENSATED CIRRHOSIS:

1. Liver transplantation is still the treatment of choice in decompensated cirrhotics.
2. HCV-infected patients who have already been accepted for liver transplantation are strongly recommended to undergo antiviral therapy with an aim to achieve pretransplantation viral eradication. Otherwise, progressive posttransplantation disease of the allograft occurs as a rule.
3. Because of the risk of development of life-threatening infection, patients who already have neutropenia or thrombocytopenia below the permissible limits (neutrophil count >1500/mm^3 & thrombocyte count >75,000/mm^3) should not be started with antiviral therapy.
4. As decompensation may actually worsen with antiviral therapy, the dose of antiviral therapy should be kept to the minimum effective i.e. 1 ìg/kg/week and 10.6 mg/kg/day for pegylated interferon and ribavirin respectively.
5. Possible indications of EPO include a fall in Hb level by >4g/dL, Hb levels of <08g/dL, and patients developing symptoms and signs of anemia (palpitations, dyspnea, easy fatigability, pallor).
6. Start EPO therapy at a lower dose of 4,000IU SQ thrice weekly (12,000IU/week) and then increase the dose depending upon the response.
7. Reduce IFN dose if neutrophil count falls to $<0.5x10^9$/L, and discontinue it if it falls to $<0.3x10^9$/L. Also, IFN dose should be reduced if platelet count falls to $<30x10^9$/L, and discontinued if it falls to $<20x10^9$/L. If despite of reducing the pegylated interferon dose to the minimum effective level, neutrophil counts of $<0.5x10^9$/L persist, G-CSF therapy may be considered.
8. Start G-CSF therapy at a dose of 30MU SQ once weekly and then adjust the dose as per the response/requirement.References:

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