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[Intervention Protocol]

Interferon for hepatocellular carcinoma

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

The objectives of this systematic Review are to try to answer the following questions based on the results of randomised clinical trials (RCTs) comparing IFN versus no intervention, placebo, or other interventions irrespective of blinding, publication status, or language:

- 1) Does IFN reduce mortality and tumour recurrences in patients with HCC when used as primary treatment?
- 2) Does IFN reduce mortality and tumour recurrences when used as adjuvant or neoadjuvant therapy in patients treated by surgical or other ablative procedures?
- 3) Does IFN cause adverse events?
- 4) Does IFN affect quality of life and health economics?

BACKGROUND

Hepatocellular carcinoma (HCC) is one of the most frequent neoplasms in the world (Okuda 2000) and one of the most frequent causes of death in patients with cirrhosis, mainly caused by hepatitis C virus (HCV) and hepatitis B virus (HBV) (Valla 2001).

Several treatments have been tested for HCC, but the results have been disappointing for several reasons. First, advanced stage of the tumour and/or the underlying cirrhosis at the time of diagnosis reduce the possibility of using more invasive approaches with higher curative rate (Llovet 2000). Only about five per cent of consecutive HCC patients in Western countries are suitable for surgical resection (Llovet 1999). Second, a high incidence of recurrence of new tumours or intrahepatic metastases of the original HCC is observed after ablation by using any of the procedures: resection, percutaneous alcohol injection, thermotherapy, embolization, etc. (Okuda 2000). Third, because of the limited supply of donor livers, orthotopic liver transplantation (OLT) - as a curative option for both HCC and the underlying cirrhosis - can only be performed on a small proportion of patients (Llovet 1999).

Primary goals to reduce the HCC death rate encompass prevention of HCC in high-risk patients and development of the best strategies to diagnose liver cancer in an early phase, selecting properly patients for the treatment. Further, we need interventions that can increase survival in patients with HCC and reduce recurrences.

IFN has antiviral effect with clearance of HCV and HBV in a variable proportion of patients (Wong 1993; Myers 2002) and has shown antitumoural activities, including inhibition of angiogenesis and antiproliferative activities (Murphy 2001). IFN is currently used to treat some malignancies like hairy-cell leukaemia (Guterman 1994) and Kaposi sarcoma (Guterman 1994) and it is under evaluation for melanoma (Grob 1998) and metastatic renal carcinoma (Mickisch 2001).

Interferon (IFN) has been tested in a variety of stages of chronic HCV and HBV related liver diseases to find out whether it reduces HCC risk development (Valla 1999; Nishiguchi 2001). Further, it has been tested in patients with advanced stages of HCC (Lai 1993; Llovet 2000), or in patients in which the primary tumour is resected (Ikeda 2000; Kubo 2001) as a component of a multimodality combination or sequential treatment.

So far, inconsistencies among published trials have been reported regarding the therapeutic effect of IFN for HCC (Lai 1993; Llovet 2000). We, therefore, will perform a systematic Review on the beneficial and harmful effects of IFN for HCC treatment.

OBJECTIVES

The objectives of this systematic Review are to try to answer the following questions based on the results of randomised clinical trials (RCTs) comparing IFN versus no intervention, placebo, or other interventions irrespective of blinding, publication status, or language:

- 1) Does IFN reduce mortality and tumour recurrences in patients with HCC when used as primary treatment?
- 2) Does IFN reduce mortality and tumour recurrences when used as adjuvant or neoadjuvant therapy in patients treated by surgical or other ablative procedures?

- 3) Does IFN cause adverse events?
- 4) Does IFN affect quality of life and health economics?

METHODS

Criteria for considering studies for this review

Types of studies

We plan to include all RCTs, either with parallel-group or cross-over design, irrespective of blinding, publication status, or language. For cross-over trials, only data from the first phase of the trial will be used. Quasi-randomised trials will be excluded.

Types of participants

Patients with HCC at any stage of the disease will be included. The presence of HCC should have been defined by histology, or cytology, or by clinical diagnosis, i.e., cirrhosis plus raised alpha-fetoprotein (AFP) > 400 ng/ml) and typical images indicating HCC on ultrasound (US), computed tomography (CT), or angiography (Okuda 2000).

Patients will be considered 'without advanced HCC' (suitable for radical therapies, i.e., resection, OLT, or percutaneous techniques) (Bruix 1997; Schafer 1999) if they have a single lesion less than five cm, or they have no more than three nodules, each being less than three cm, are in Child-Pugh (Pugh 1973) class A or B, and are without extrahepatic spread, vascular invasion, or portal thrombosis. Patients who do not fit these criteria will be considered with 'intermediate-advanced-HCC' (Bruix 2001).

Patients at risk of HCC but without actual cancer will not be considered.

Types of interventions

- IFN (any type, dose, and schedule) versus placebo, no intervention, supportive therapy, or other treatments.
- IFN (any type, dose, and schedule) plus other intervention versus the same other intervention.

IFN will be defined as the primary intervention if used in patients not suitable for surgery, local ablation of the tumours, or embolization.

IFN will be defined as adjuvant or neo-adjuvant intervention if used in patients in which other interventions, aimed to cure the primary tumours, were used: surgical ablation (resection, OLT), local ablation (by percutaneous ethanol or acid acetic injection or radiofrequency, etc), or embolization of the primary tumour(s).

Types of outcome measures

The following outcome measures will be evaluated:

1. Number of patients dying (primary outcome measure). When the number is not reported by the authors we will contact them for further information.
2. Objective response, according to the World Health Organization (WHO 1981) criteria (See Appendix 1). When the authors have used different definition criteria, we will report them.
3. Number of patients who had HCC recurrence develop. Recurrence is defined as diagnosis of new HCC in patients in whom no signs of HCC were detected by using US and/or CT scan and in whom AFP fell below the upper limit of the reference range after the treatment had been applied. The diagnosis of new HCCs will be

made according to the diagnostic criteria described above under 'Types of participants'.

4. Number and type of adverse events, defined as any untoward medical occurrence in a patient in any of the two intervention groups. This occurrence should not necessarily have a causal relationship with the treatment, but did, however, result in a dose reduction or discontinuation of treatment. We have defined serious adverse events according to the ICH guidelines (ICH-GCP 1997) as any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or congenital anomaly/birth defect, and any important medical event which may have jeopardise the patient or requires intervention to prevent it. All other adverse events will be considered non-serious.

5. Quality of life: improvement of performance status, disappearance or reduction of pain, or whatever the investigators defined as quality of life.

6. Health economics: length of hospitalisation, cost for procedure, or whatever the investigators defined costs as in relation to any benefit.

Search methods for identification of studies

Relevant studies will be identified by searching *The Cochrane Hepato-Biliary Group Controlled Trials Register*, *The Cochrane Central Register of Controlled Trials Register* in *The Cochrane Library*, *MEDLINE*, and *EMBASE*.

Because a single search strategy could miss relevant RCTs, we will use several search strategies to obtain a result as complete as possible. We will combine 'topic only' and 'study design focused' strategies (Handbook 2000).

The searches in *The Cochrane Hepato-Biliary Group Controlled Trials Register* and *The Cochrane Central Register of Controlled Trials Register* in *The Cochrane Library* will be performed using the search terms: interferon and hepatocellular carcinoma.

The search strategy for *MEDLINE* and *EMBASE* include the terms: (interferon [MESH] or interferon [TEXT WORD]) or interferon [SH] AND (hepatocellular carcinoma [TEXT WORD] or carcinoma, hepatocellular [MESH]) AND (meta-analysis) [PTYP] or (systematic review) [PTYP] or (randomized controlled trial [SH] or random* [WORD]).

Abstracts presented at The European Association for the Study of the Liver (EASL) and at The American Association for the Study of the Liver Diseases (AASLD) will be obtained through The Cochrane Hepato-Biliary Group, which is handsearching 'Journal of Hepatology' and 'Hepatology'. Furthermore, abstracts presented at the Digestive Disease Week and World Congresses will be handsearched by perusing directly the abstract books.

Manufacturers of IFN and authors of the included publications will be asked to provide more information on any trial of which they may know.

Data collection and analysis

The meta-analysis will be conducted according to this protocol following the recommendations given by The Cochrane Collaboration, Sacks et al. (Sacks 1987), and Egger et al (Egger 1997).

Methodological quality

Internal validity, that is, the extent to which systematic error (bias) is minimised in RCTs (Jüni 2001), will be addressed by searching potential bias sources in the individual trials. We will explore biases by addressing the quality of the retrieved RCTs. The quality will be assessed by using validated individual components which have been associated with empirical evidence of bias (Kjaergard 2001; Jüni 2001) including generation of the allocation sequence, allocation concealment, and blinding. Furthermore, completeness of reporting on withdrawals and dropouts will be analysed as well as the use of intention-to-treat analyses explored. Each component will be judged as adequate or not adequate following the classification reported by Kjaergard et al. (Kjaergard 2001) (see details in Appendix 2). High quality RCTs will be classified as those with adequate generation of the allocation sequence, adequate allocation concealment, double blinding, reporting of number and reasons of lost to follow-up, and use of intention-to-treat analyses.

In addition, we will address:

- the equivalence within trial treatment groups of: baseline variables; inclusion and exclusion criteria; treatments during the trial; intervals of checking for tumour recurrences, procedures used for searching for tumour recurrence, and diagnostic criteria for HCC recurrences; completeness and time of follow-up of trial treatment groups. To address the balance between groups for prognostic factors, we will report the mean age in the comparative groups and the proportion of the variables with a well-known predictive role (Schafer 1999; Colombo 2000; Johnson 2000; Llovet 2000): male sex, coinfection with HBV and HCV, alcohol abuse, stage of HCC expressed by a score system (CLIP 1998; Ueno 2001) or by individual indicators (size and number of tumours; evidence of local or distant spread; presence of vascular invasion; portal thrombosis; AFP level); severity of liver dysfunction as expressed by the Child-Pugh classification (A-B-C) (Pugh 1973), or by the presence of individual indicators of liver disease stage (ascites; encephalopathy; history of bleeding), or stage of tumours and liver dysfunction as expressed by Okuda's classification (Okuda 1985); performance status (Sorensen 1993).
- possible sources and reasons for heterogeneity (if any) of the results will be explored (Egger 1997).

Statistical analyses

We will perform all analyses according to the intention-to-treat method. For all outcome measures, we will consider patients with incomplete or missing data as 'treatment failures' in a worst-case scenario analysis and as 'not a treatment failure' in a best-case scenario analysis. The statistical package (RevMan and MetaView) provided by The Cochrane Collaboration will be used.

The meta-analysis will be performed using the DerSimonian and Laird random effects model and a Mantel-Haenszel fixed effect model to obtain a combined estimate of the relative risk (RR) and a corresponding 95% confidence interval (CI) for each outcome measure at the end of the follow-up and at one and two years. Heterogeneity will be addressed also by visual display of the results. To assess the public health impact of IFN in treating HCC, we will calculate the pooled risk differences and 95% CI. The number needed-to-treat (NNT) will be calculated by taking the inverse of the pooled risk difference if a narrow range of baseline risk and an equivalent length of the follow-up have been detected in the studies so that an absolute measure could be meaningful. Because the NNT is related to the baseline risk (Smeeth 1999), we will report

the NNT relevant to the baseline risk of specific patient group as well as follow-up time.

The duration of survival, quality of life, and health economic data will be assessed with a weighted mean difference (WMD) if continuous data are reported.

The trials will be grouped in:

- trials in which IFN was used as primary intervention;
- trials in which IFN was used as adjuvant or neoadjuvant intervention.

Potential causes for heterogeneity will be explored by performing sensitivity analyses in respect to: 1) influence of methodological quality of the trials; 2) influence of stage of HCC; 3) duration of treatment and length of follow-up; 4) presence of a dose-response effect; 5) influence of ethnic origin of patients. The analyses will be performed after the exclusion of appropriate trials from the group of included trials: 1) exclusion of low quality trials and cross-

over trials; 2) exclusion of studies enrolling patients with 'advanced HCC'; 3) exclusion of studies with a duration of the treatment below the median treatment duration in the included studies; 4) exclusion of studies with a total amount of IFN below the median dose of IFN administered in the included studies. Furthermore influence of etiology of the underlying cirrhosis and ethnicity will be addressed analysing separately studies enrolling patients mostly (> 70 per cent) with HBV, HCV, or mostly (> 70 per cent) with non-viral liver disease and studies from Eastern and Western countries.

Funnel plot will be used to address graphically the presence of biases ([Egger 1997a](#)).

ACKNOWLEDGEMENTS

We thank the patients who participated in the reviewed trials and the researches who conducted the reviewed trials.

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APPENDICES

Appendix 1. World Health Organization criteria

Response to treatment will be defined following the World Health Organization (WHO) (WHO 1981) criteria:

Complete response: no evidence of neoplastic disease.

Partial response: reduction in total tumour load of greater than 50 per cent.

No change: reduction of tumour load by less than 50 per cent or increase of less than 25 per cent

Progressive disease: increase of tumour load by greater than 25 per cent.

Appendix 2. Bias components

Generation of the allocation sequence

- Adequate: if sequences are suitable to prevent selection bias: table of random numbers, computer-generated random numbers, tossing a coin or similar
- Inadequate: if it is not described or if sequences could be related to prognosis: case record number, date of birth, day of the week, or similar (quasi-randomised trials). Such quasi-randomised studies will be excluded.

Allocation concealment

- Adequate: when the following approaches have been used: centralised randomisation (e.g., allocation by a central office unaware of subject characteristics); pre-numbered or coded identical containers which are administered serially to the participants; sequentially numbered, sealed, opaque envelopes; and other approaches in which the description could reassure that the person who generated the allocation scheme did not administer it.
- Unclear: when studies do not report any concealment approach.
- Inadequate: when the following modalities were used: alternation; the use of case record numbers, dates of birth or day of the week, and any procedure that is entirely transparent before allocation, such as an open list of random numbers. (D) Not used.

Blinking (Clarke 2000)

- Adequate: when it is 'double blind' (both participants and investigators are unaware of what intervention the participants are given).
- Inadequate' when it is 'single blind' (only the participants are unaware of the intervention) or 'unblind'.

The blinding for investigators refers to those (care providers, radiologist etc) who assess the outcomes of treatments and to those who do interpretation of imaging and decision of subsequent verification.

Handling of dropouts and withdrawals:

- Adequate' when numbers and reasons were described.
- Inadequate' when number or reasons were not described.

Intention-to-treat analysis: inclusion of all randomised patients in the analyses.

HISTORY

Protocol first published: Issue 4, 2002

Date	Event	Description
28 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

RGS drafted the protocol, will select trials, extract data, assess methodological quality, and draft the Review. CG revised the protocol, will select trials, and revise the Review. LP revised the protocol, will extract data, and revise the Review.

DECLARATIONS OF INTEREST

None known, apart from the fact that Rosa G. Simonetti and Luigi Pagliaro have previously performed a meta-analysis (Simonetti 1997) on the treatment of hepatocellular carcinoma.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Copenhagen, Denmark
- Azienda Ospedaliera 'V. Cervello', Palermo, Italy

External sources

- The Danish Medical Research Council's Grant on Getting Research into Practice (GRIP), Denmark
- The Copenhagen Hospital Corporation Medical Research Council's Grant on Getting Research into Practice (GRIP), Denmark

NOTES

The protocol is out of date and does not meet the current methodological standards of Cochrane.