

IMPACT OF NEUTROPENIA IN CHEMOTHERAPY EUROPEAN STUDY GROUP

INC-EU Study Group Hosts Breast Cancer Workshop in San Antonio

The 25th Annual San Antonio Breast Cancer Symposium, held in Texas, USA, provided an ideal opportunity for the Impact of Neutropenia in Chemotherapy European Study Group (INC-EU) to host an affiliated workshop, and to hold its second INC-EU Study Group meeting. Over 50 delegates attended the workshop, Controversies in Adjuvant Chemotherapy for Primary Breast Cancer, and heard the latest news on treatment issues relating to breast cancer, chemotherapy and the risk of neutropenic complications.

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An experienced panel of international experts presented a compelling argument for the pre-emptive use of growth factors in patients at greatest risk of developing neutropenic complications as a result of their myelosuppressive chemotherapy.

According to Professor Gary Lyman from the University of Rochester in the USA:

- Breast cancer mortality has declined in recent years as a result of early detection and improved treatment
- Adjuvant chemotherapy improves survival in women with early-stage breast cancer, but optimal outcomes are only achieved with sustained standard dose intensity
- Breast cancer adjuvant therapy is frequently associated with neutropenia, which leads to dose reductions and dose delays

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- G-CSF in the adjuvant setting reduces the incidence of severe neutropenia and helps to sustain dose intensity
- Promising advances to improve both the effectiveness and cost-effectiveness of G-CSF are in development:
 - Clinical prediction models will help to select high-risk patients that will benefit most from targeted G-CSF therapy
 - Longer-acting and more potent G-CSF treatments will improve dosing convenience and allow more patients to benefit from growth factor support
- Supportive measures, including G-CSF, should be used in selected women in order to sustain scheduled dose on time

Increasing Activity Levels in 2003

The INC-EU also reported news of its planned pan-European chemotherapy audit, which is due to commence in Q3 2003, and should help in the development of a validated risk assessment tool. In addition to initiating this ambitious European study, 2003 will see an increasing level of activity from the INC-EU, including the launch of its website, regular newsletters, publication of the San Antonio workshop proceedings in a peer-review journal, and the development of a neutropenia audit pack (Figure 1).



Figure 1

Dose-Dense Chemotherapy Improves Outcomes in Breast Cancer and Lymphoma

Evidence is mounting that dose-dense strategies in the treatment of breast cancer and lymphoma can significantly improve clinical outcomes. Pre-emptive use of G-CSF in patients receiving more intensive dosing schedules reduces the risk of neutropenia associated with both conventional and dose-dense chemotherapy regimens, allowing more patients to achieve optimal outcomes from a more aggressive approach to treatment.

At this INC-EU Study Group meeting, Professor Gary Lyman, from the University of Rochester Medical Center in the USA, outlined the results of a landmark (CALGB 9741) study by Citron M, Berry D, Cirincione C et al, and the potential impact of this study on improving outcomes. Presented for the first time at the plenary meeting, the study demonstrated that 2-weekly administration of doxorubicin 60 mg/m²/paclitaxel 175 mg/m²/cyclophosphamide 600 mg/m² with filgrastim support produced a significant improvement in disease-free survival and overall survival compared with a 3-weekly schedule without G-CSF support¹. No differences were seen in

CALGB 9741 study summary ¹

- 2005 women with node-positive primary breast cancer
- Median age: 50 years
- At 3 years, the dose-dense strategy (i.e. 2-weekly administration + G-CSF) was superior to conventional dosing (i.e. 3-weekly dosing – G-CSF):
 - 26% reduction in risk of disease recurrence (p=0.0072)
 - 31% improvement in risk of mortality (p=0.014)
- Dose-dense schedule + G-CSF caused fewer cases of neutropenia than conventional dosing without G-CSF

outcomes whether the chemotherapy was administered sequentially or concurrently.

According to Professor Lyman, although other retrospective studies had shown that patients who received at least 85% of their planned dose intensity had better outcomes than those who did not², the CALGB 9741 study was the first randomised, controlled clinical trial



Prof Gary Lyman presented studies demonstrating clear benefits of intensive dosing strategies

to show conclusive benefits for reducing the interval between chemotherapy doses. This, he said, was extremely encouraging, and very likely to result in changes to international clinical guidelines and to clinical practice in the future.

‘What impressed me most about this study, was that toxicity was not increased in the dose-dense arms when G-CSF support was given’, said Professor Lyman. ‘In fact, use of G-CSF actually reduced neutropenic events in patients receiving 2-weekly chemotherapy compared with those on a conventional 3-weekly dosing schedule.’

Efficacy of G-CSF in World Literature

The CALGB 9741 study confirms the findings of previously reported randomised controlled trials in which G-CSF was given as a prophylactic measure in patients being treated for solid tumours and lymphomas. Professor Lyman presented the results of a meta-analysis of eight randomised controlled trials involving over 1100 patients, which demonstrated that prophylactic use of G-CSF resulted in a 62% reduction in the odds of febrile neutropenia, and significantly reduced the likelihood of a dose reduction or dose delay³ (Figure 2). Since febrile neutropenia and reductions in dose intensity are both associated with poorer clinical outcomes, Professor Lyman suggested that prophylactic G-CSF be considered for patients at greatest risk of developing neutropenia and its complications.

‘We have learnt from randomised clinical trials that dose intensity does matter and does affect long-term outcomes in these patients,’ explained Professor Lyman. ‘In order to maintain full dose intensity, haematopoietic growth factors should certainly be considered in selected women receiving adjuvant breast cancer therapy.’

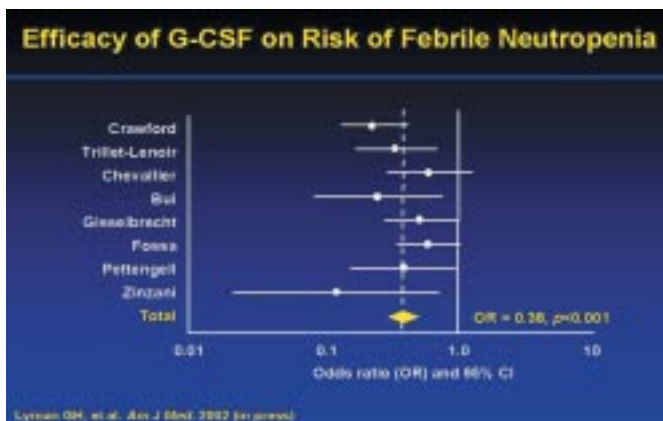


Figure 2

New dose-dense studies in lymphoma

Two new studies have recently been reported that show similar benefits of dose-dense strategies in the treatment of lymphoma:

- Diehl *et al* have claimed that, in the treatment of advanced Hodgkin's disease, a new, 3-weekly-cycle of BEACOPP, with moderate dose escalation and G-CSF support, greatly improved tumour control and overall survival, with manageable toxicity, compared with the standard regimen and with COPP alternating with ABVD⁴
- Pfreundschuh *et al* also claimed that 2-weekly CHOP, with G-CSF support, improved response rates, TTF and overall survival compared with CHOP-21 in elderly patients with aggressive NHL. The investigators suggest that CHOP-14 + G-CSF should now be the standard regimen for these patients⁵

European Audits Reveal Consistency in Breast Cancer Care

A combined analysis of data from three clinical practice audits in Europe has revealed a consistency between countries in treatment approaches used in primary breast cancer (Figure 3). Audits conducted in the UK, Belgium and Spain show widespread use of anthracycline-containing treatment regimens, a relatively high incidence of febrile neutropenia, and a broadly inadequate use of G-CSF support. This, said Professor Robert Leonard from the South West Wales Cancer Institute in the UK, probably explained why chemotherapy dose reductions and delays were commonplace in all countries audited to date and why so many women are admitted to hospital suffering from neutropenic complications.

‘These individual practice audits, which are a true reflection of what is really happening to most women with primary breast cancer in Europe, show that neutropenia is still a significant clinical issue in the treatment of this condition,’ Professor Leonard told the meeting. ‘Approximately 30% of women have a chemotherapy dose delay, dose reduction or febrile neutropenic event and, as a result, between 5 and 10% of women are admitted to hospital with febrile neutropenia, and at least one in six women are receiving a less than ideal chemotherapy dose intensity.’



Prof Robert Leonard, “Neutropenia is still a significant clinical issue”

received a standard CMF regimen, and 35% received concurrent radiotherapy. Febrile neutropenia was reported in an average of 6.1% of patients across Europe, with individual countries ranging between 3.2-7.4%.

Dose reductions and dose delays appear to be strategies commonly applied to overcome toxicity issues, said Professor Leonard. In European countries 20% of patients had their dose reduced, while 39% of patients had a dose delay (Figure 4).

Results from within Europe also mirror those reported in a large USA audit, which involved over 20,000 women with primary breast cancer. Treatment patterns were comparable across Europe and the USA and a similar number of women in the USA experienced neutropenic complications and dose reductions and delays.

Low G-CSF use across the board

In all European countries audited so far, G-CSF use is low, with only 15% of women receiving any growth factor support during their chemotherapy. In contrast, in the US, where cost constraints are less of an issue, 27% of women received G-CSF support (Figure 5).

‘Despite differences in the methodologies used in each of these retrospective audits, similarities have emerged across Europe and there appears to be inadequate use of G-CSF to support women receiving chemotherapy for primary breast cancer’, said Professor Leonard. ‘I think a prospective European study which attempts to measure outcomes in a uniform manner is likely to support the argument that we should be getting much more aggressive with our interventions.’

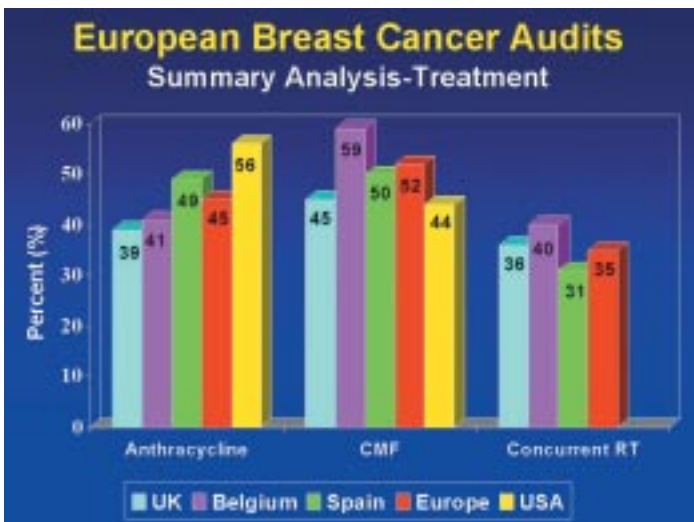


Figure 3

European clinical practice

To date, over 2,000 women with primary breast cancer have been assessed in individual European audits. Of these women, 45% received an anthracycline-containing regimen, 50%

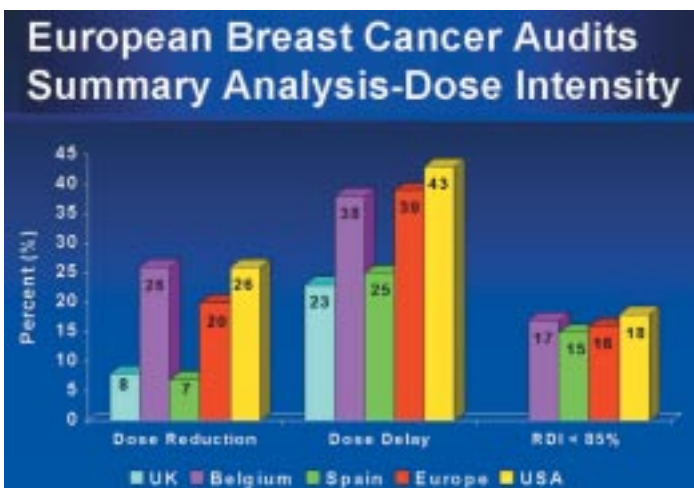


Figure 4



Figure 5

Developing a Neutropenia Risk Assessment Model

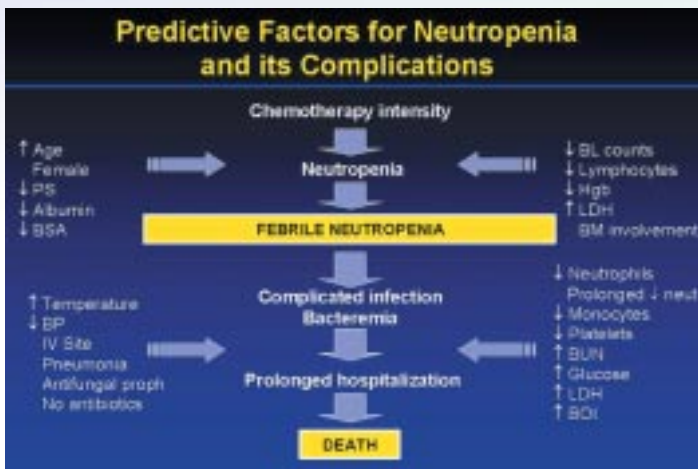


Figure 6

The development of a validated neutropenia risk assessment model remains a priority for the INC-EU and its US counterpart, the ANC. Despite the fact that chemotherapy-induced neutropenia is a well-recognised and common complication of chemotherapy, use of colony-stimulating factor - which significantly reduces the risk of neutropenic complications - is still sub-optimal in most countries. A reliable neutropenia risk model which could predict which patients are at greatest risk of developing this complication would, therefore, be invaluable in helping physicians to target prophylactic G-CSF and other supportive care at those patients most likely to require it.

According to Professor Gary Lyman, systematic retrospective analyses of published studies have already established a number of neutropenia risk factors (Figure 6), including:

- First-cycle absolute neutrophil count (ANC) nadir
- First-cycle haemoglobin reduction
- Concurrent radiotherapy

However, although retrospective analyses provide a firm foundation upon which to develop provisional clinical prediction models, prospective studies are required in order to build accurate and reliable prediction tools. To this end, the ANC and INC-EU are conducting major country-wide prospective registry studies to establish what is really happening in clinical practices around the world.

Progress in the USA

The ANC Study Group, based in the USA, is now well on target for enrolling patients into its prospective study, which started recruiting in March 2002. To date, 80 diverse community oncology practices in the USA have joined the study, and over

700 patients have now been registered. Data are being collected on treatment practices in five major malignancies: breast, lung, colonic and ovarian cancers, and lymphoma, covering 12,000 variables.

The aims of the study are to:

- Estimate the frequency of grade 3 and 4 neutropenia associated with common myelosuppressive chemotherapy regimens
- Estimate the frequency and severity of neutropenic events as indicated by chemotherapy dose reduction, chemotherapy dose delays and febrile neutropenia
- Define and quantify the relationship between neutropenic complications and chemotherapy dose delays and reductions
- Identify the relationship between treatment variables, patient comorbidities and the frequency and severity of neutropenic events
- Develop and validate disease-specific risk models for identifying patients at increased risk of neutropenic complications

A tremendous resource

Despite the major logistical challenges associated with running such a large and complex community-based study, Professor Gary Lyman - Director of the ANC Co-ordinating Centre - believes that the results will certainly justify the effort required by Study Group members and the clinical investigators.

'No-one believed that this would ever be easy', Professor Lyman told the INC-EU Study Group, 'but despite a few logistical issues, I have to admit that I am very satisfied with how things have gone.'

'We've had excellent compliance, the data being generated is very comprehensive, and I think this will be a tremendous resource that we will be challenging for years to come.'

ANC Prospective Registry

- Recruitment began March 2002
- 80 community oncology practices already enrolled
- 720 patients registered to date
- Data being collected in cancers of the breast, lung, colon, ovary, and in lymphomas

Early Results in Breast Cancer

An early analysis of data collected by the ANC on pre-treatment and early-chemotherapy-cycle factors in over 200 patients with breast cancer, was presented as a poster in San Antonio⁶. The study included a wide cross-section of patients at different disease stages receiving a variety of treatment regimens.

Key findings from the preliminary analysis presented by Prof Gary Lyman:

- 41% of patients became neutropenic during their first chemotherapy cycle (ANC nadir $<1 \times 10^9/L$)
- 26% of patients developed severe neutropenia during their first chemotherapy cycle (ANC nadir $<0.5 \times 10^9/L$)
- Hb dropped by an average of 1.3 g/dL in the first chemotherapy cycle
- Cycle 1 ANC nadirs were lowest in patients:
 - with earlier-stage disease (stages I-III)
 - aged >65 years
 - treated with anthracycline-based regimens

According to the investigators, these early results confirm the feasibility and promise of this approach to risk

modelling, although they say further analysis and follow-up are still required.

Developing a pan-European study

The success of, and experience gained from, the US prospective registry has helped greatly in the planning and development of a similar pan-European study, which it is hoped will commence in the autumn of 2003. The study protocol has now been drafted and is currently being refined by members of the INC-EU Study Group. Plans to seek input and involvement of established European clinical research groups are being developed.

Although the objectives and goals of the European study will be similar to those of the US registry outlined above, the European study will be restricted to evaluating the outcomes in the adjuvant treatment of breast cancer and the treatment of Hodgkin's lymphoma and NHL.

Maintaining a close relationship with the US

Dr Ruth Pettengell, a member of the INC-EU Study Group, has been working closely with the ANC Study



Dr Ruth Pettengell believes it is vital to keep a close relationship with US colleagues

Group to ensure cross-fertilisation of ideas and best practice. She believes it is vital to keep a close liaison across the Atlantic and to do everything possible to ensure that the final datasets can be contrasted and, ideally, combined.

'We can learn a great deal from our colleagues in the USA as we develop the protocol for the European study and start recruiting,' she told INC-EU Study Group members.

'Since our study objectives are similar to those of the US, we should work closely together to optimise the output and ensure that we maximise the exposure of the data through conference presentations and publications.'

INC-EU Prospective Study

- Draft protocol currently being refined by Study Group members
- Anticipated start: Autumn 2003
- Data being collected in the adjuvant treatment of breast cancer, NHL and Hodgkin's lymphoma
- Objective: Estimate frequency and severity of neutropenia events associated with chemotherapy

INC-EU Endorses European Neutropenia Audit Package

The INC-EU has endorsed the principles of, and need to develop, a neutropenia audit package to help European oncology centres assess the quality and outcomes of their own management practices and to make improvements where necessary. Dr Christian Jackisch has developed the idea on behalf of the INC-EU, since he believes that neutropenia is both an under-appreciated and often avoidable consequence of some chemotherapies.

The neutropenia audit package would consist of an 'off-the-shelf' tool containing everything needed for oncology centres to conduct their own practice audits and, with the help of the INC-EU, to analyse their own chemotherapy dose delivery and the impact of neutropenic events on dose intensity. A feedback system would be initiated to ensure that centres knew how they were operating compared with other practices and that improvements were effected where they were required.

Simple data collection

According to Dr Jackisch, the secret to successful auditing in this condition would be to keep the protocol as simple as possible in

order to encourage use and completion. He said audits should include all chemotherapy regimens and all cancers, and centres would be offered the opportunity to obtain a detailed analysis of their own data on individual regimens and tumour types.

'I think it is really important that oncology centres assess how effective their chemotherapy dose delivery is - especially in the adjuvant breast cancer setting and in the treatment of lymphoma,' said Dr Jackisch. 'We would want them to look especially closely at the total dose delivered and the total dose intensity, compared with what was planned before treatment began.'

Key features of the neutropenia audit package:

- Simple data collection to encourage use and completion of audit
- The facility to include all regimens and tumour types, but only selected ones will be analysed in detail
- Results from the audit will enable individual centres to evaluate delivered dose compared with other centres
- Data from centres may be combined to create a larger dataset



Dr Christian Jackisch. "Neutropenia is an often avoidable consequence of some chemotherapies."

INC-EU Audit Packages

The audits will enable oncology centres to:

- Assess their own chemotherapy dose delivery
- Evaluate the impact of neutropenic events on chemotherapy
- Monitor the use of growth factors and support measures
- Produce data enabling centres to compare their results with others
- Implement a feed-back system to improve practice

Novel Neutropenia Therapies in Development

The development of predictive risk models and the availability of new-generation molecules for the prevention of neutropenia should significantly improve the outcomes for cancer patients in the future.

Using targeted approaches to prevent neutropenia in at-risk patients should ensure that more patients achieve optimal chemotherapy doses and related clinical benefits and fewer patients are admitted to hospital with neutropenic complications.

Dr Jeffrey Crawford from the Duke University Medical Center in the USA outlined the clinical development programme for pegfilgrastim - a new, long-acting form of filgrastim - which can be administered as a single, fixed-dose injection just once per cycle.

According to Dr Crawford, advantages of pegfilgrastim over current G-CSF treatments include:

- Superior efficacy in reducing febrile neutropenia than daily filgrastim

- A single, fixed-dose 6 mg injection for all patients, rather than up to 11 daily injections per chemotherapy cycle
- Once-per-cycle dosing
- A self-regulating, neutrophil-mediated clearance, with serum levels decreasing as ANC recovers

Pegfilgrastim is well tolerated

In large-scale clinical trials, pegfilgrastim was as well tolerated as filgrastim, with similar numbers of patients reporting bone pain, which was readily controlled using non-narcotic analgesics (Figure 7).

Professor Robert Paridaens from the Department of Oncology at the University Hospital Gasthuisberg in Leuven, Belgium, believes pegfilgrastim will greatly simplify the management of chemotherapy-induced neutropenia and



Dr Jeffrey Crawford outlined the clinical development programme for pegfilgrastim

should help in sustaining dose intensity in the treatment of breast cancer. 'Neutropenia impacts on both the quality and costs of chemotherapy and is the commonest cause of life-threatening complications associated with treatment,' he said. 'My deep conviction is that pre-emptive strategies are the most clinically and cost-effective approaches, with at-risk patients being identified and treated before they develop any neutropenia.'



Prof Robert Paridaens. "Pre-emptive strategies are the most clinically and cost-effective approaches to managing neutropenia."

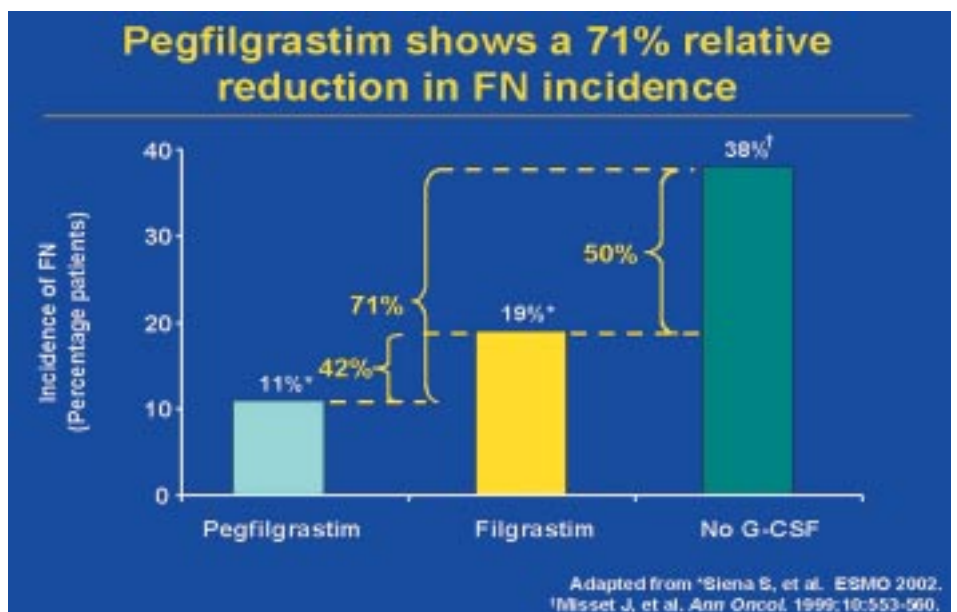


Figure 7

- Pegfilgrastim has been available in the USA since April 2002
- Pegfilgrastim will become available in many European countries during 2003

INC-EU Study Group Website for Neutropenia News and Information

Healthcare professionals with an interest in neutropenia will soon have access to all the latest news, clinical guidelines and INC-EU Study Group information on an INC-EU dedicated website. www.inceu.org is currently under development and hopes to serve the information needs and provide a forum for exchange of views of clinical investigators, registered health professionals and members of the public.

Registered healthcare professionals will have secure access to:

- INC-EU publications
- Newsletters
- Reviews and articles
- Recommended reading lists
- Conference abstracts
- Treatment guidelines/positioning papers
- Conference scheduler

INC-EU investigators will also be able to access:

- Study protocols
- Manuscripts under development
- Newsletter drafts
- Patient record databases
- Discussion forums

Public information about the INC-EU and useful web site links will also be provided.

The website will be built with several secure, restricted-access areas and will be updated regularly. All content will be approved by the INC-EU Study Group and managed by dedicated website co-ordinators.

Other useful neutropenia-related websites:

- www.neutropenia.ca
- www.bymyside.com
- www.asco.org

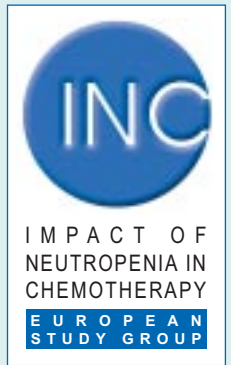
Future INC-EU Study Group Meetings in 2003

The INC-EU plans to increase awareness of neutropenia and its consequences throughout 2003 by holding the INC-EU Study Group meetings in association with international conferences.

INC-EU Study Group meetings will be held at:

- **Primary Therapy of early Breast Cancer: 8th International Conference, St Gallen (11 March 2003)**
- **ASCO, Chicago (30 May 2003)**
- **ECCO/EONS, Copenhagen (20 September 2003)**
- **6th Febrile Neutropenia Symposium, Brussels (17 December 2003)**

If you have something to say, you can contact the INC-EU co-ordinating centre by phone: +44 1256 884000 or e-mail: info@inceu.org



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