

## IMPACT OF NEUTROPENIA IN CHEMOTHERAPY EUROPEAN STUDY GROUP

The mission of the Impact of Neutropenia in Chemotherapy European Study Group (INC-EU) is to raise awareness and prevent the occurrence of chemotherapy-induced neutropenia (CIN), by assessing the incidence, consequences and patient risk factors, and by identifying and developing accurate prediction models for CIN, such that high-risk patients can be effectively targeted for preventative measures.

### INC-EU PUBLISHES RESULTS OF THE PROSPECTIVE STUDY

The INC-EU Study Group recently achieved a number of key milestones; a manuscript reporting the first results from the Prospective Observational European Neutropenia Study has been published online<sup>1</sup> and two abstracts on risk factors for febrile neutropenia (FN) were also published at the ASH 2007 meeting<sup>2,3</sup>.

#### Key findings from the Prospective Study

- **FN rates** were 6% for breast cancer, 22% for non-Hodgkin lymphoma (NHL), and 15% for Hodgkin lymphoma (HL) patients.
- **Neutropenic events** were most frequent during the first chemotherapy cycle.
- Over 20% of breast cancer patients and 30% of lymphoma patients received relative dose intensity (RDI)  $\leq$  85%.
- **Risk factors for low RDI** in both breast cancer and lymphoma patients were identified as age  $\geq$  65, Eastern Cooperative Oncology Group (ECOG) performance status  $>$  1 and cycle 1 FN.
- **Risk factors for cycle 1 FN** and FN in any cycle of chemotherapy in a subset of patients with NHL were identified as: older age, lower weight, increasing planned cyclophosphamide dose, a history of previous chemotherapy or recent infection, and low baseline albumin.
- **Prophylactic colony-stimulating factor** (CSF) use had a protective effect.

#### Recent INC-EU publications

##### Neutropenia occurrence and predictors of reduced chemotherapy delivery: results from the INC-EU prospective observational European neutropenia study.

Ruth Pettengell, Matthias Schwenkglenks, Robert Leonard, André Bosly, Robert Paridaens, Manuel Constenla, Thomas D. Szucs and Christian Jackisch. *Support. Care Cancer*. 2008; **Open access:** DOI 10.1007/s00520-008-0430-4.

##### A prospective multivariate analysis of risk factors associated with occurrence of febrile neutropenia in any cycle in NHL patients receiving chemotherapy.

Ruth Pettengell, André Bosly, Thomas D. Szucs, Christian Jackisch, Robert Leonard, Robert Paridaens, Manuel Constenla and Matthias Schwenkglenks. *Blood* 2007; 110(11): Abstract 4447.

##### Risk factors associated with occurrence of febrile neutropenia in NHL patients in the first cycle of chemotherapy - A prospective multivariate model.

Ruth Pettengell, André Bosly, Thomas D. Szucs, Christian Jackisch, Robert Leonard, Robert Paridaens, Manuel Constenla and Matthias Schwenkglenks. *Blood* 2007; 110(11): Abstract 1372.

See inside for more details.

### NEWS BULLETIN



Two new interactive tools are available to help assess the risk of haematotoxicity in clinical practice:

- The FN risk assessment tool (available on [www.inceu.org](http://www.inceu.org)) is based on ASCO and EORTC guidelines. Clinicians are guided through a series of steps to help assess the level of FN risk to patients according to tumour type and chemotherapy regimen and to identify when CSF support is recommended.
- Ziepert et al.<sup>4</sup> developed and validated a model that helps assess the risk of haematotoxicity in patients with aggressive NHL receiving CHOP-like regimens ([www.toxcalculator.com](http://www.toxcalculator.com)). Risk can be calculated based on pre-treatment factors alone, or in combination with information on haematotoxicity during the first chemotherapy cycle.

## NEW PUBLICATIONS FROM THE INC-EU PROSPECTIVE STUDY

The first manuscript from the INC-EU Prospective Study<sup>1</sup> reports data from breast cancer and lymphoma patients recruited from 66 practices in five European countries. Patients eligible for inclusion were starting a new myelosuppressive chemotherapy sequence with at least 4 cycles planned.

### Incidence of CIN, FN and dose limitations

Data from 444 breast cancer patients were analysed, the majority of whom received anthracycline-based regimens. Primary CSF prophylaxis was provided to 9% of patients and the rate of FN was generally low at 6%, although **grade 4 CIN occurred in 34% of patients**. Over 20% of patients did not receive chemotherapy as planned, experiencing reductions and delays in their chemotherapy (Figure 1). Dose reductions and low RDI were more common in patients who experienced grade 4 neutropenia or FN.

Of 305 lymphoma patients, 240 had a diagnosis of NHL and 65 had HL. The majority of NHL patients (74%) were treated with CHOP-21-like regimens and primary CSF prophylaxis was provided to 12% of these patients. **The rate of FN with CHOP-21-like regimens was 22%**, with over 50% of patients experiencing grade 4 CIN. One third of NHL patients undergoing CHOP-21-like chemotherapy did not receive treatment as planned (RDI  $\leq$  85%). Fifteen percent of HL patients experienced FN, 40% developed grade 4 CIN, and 30% received RDI  $\leq$  85%. Across both breast cancer and lymphoma patients, the highest rates of CIN and FN were seen in the first cycle of chemotherapy.

### Model of risk factors for low RDI

Increased awareness of factors that are associated with chemotherapy dose limitations can assist clinicians in identifying at-risk patients and facilitate patient management. In a multivariate analysis, age  $\geq$  65 years, ECOG  $>$  1 and previous FN were identified as **risk factors for RDI  $\leq$  85%**. In lymphoma patients, primary CSF prophylaxis was associated with a decreased risk of low RDI.

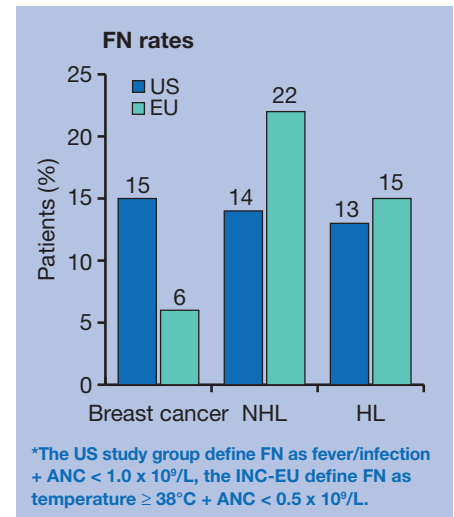
### Comparison with results from the ANC

The INC-EU has a good working relationship with their US counterpart, the Awareness of Neutropenia in Chemotherapy Study Group (ANC). Professor Gary Lyman and other members of the ANC provided advice on the initial set-up of the Prospective Study. Comparison of results from the INC-EU and the ANC reveals that FN and CIN not only remain frequent in European practice, but also in the US. In a prospective nationwide study<sup>5</sup>, rates of FN in 1,138 breast cancer patients were slightly higher than in the European study, at 15% (Figure 2); although a broadly similar number of patients (42%) experienced neutropenia at some point during their treatment. Among 257 NHL and 55 HL patients in the US study, trends in FN and CIN rates generally mirrored those seen in the INC-EU study, but were slightly lower.

### Model of risk factors for FN in NHL patients

Analysis of a subset of 240 NHL patients from the Prospective Study found that FN predictors in the **first cycle of chemotherapy** were<sup>2</sup>:

Figure 2: FN\* rates in US and European breast cancer and lymphoma patients<sup>1,5</sup>



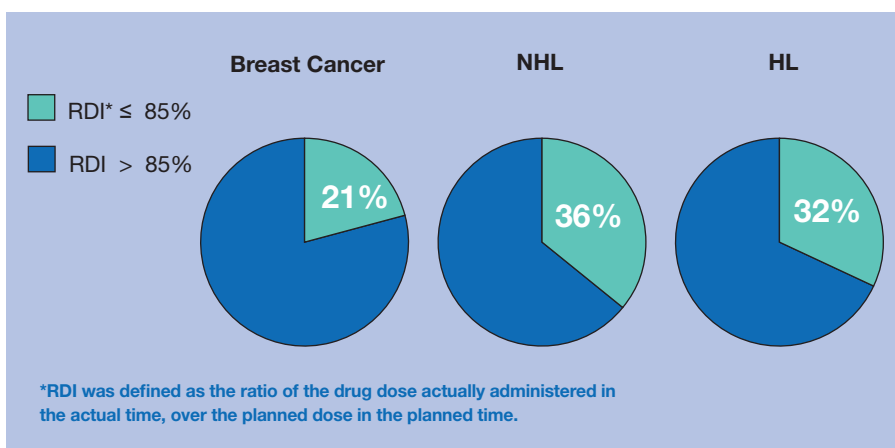
- low baseline albumin
- high baseline alkaline phosphatase
- low glomerular filtration rate or high age
- low height or weight
- recent infection
- previous chemotherapy
- high planned cyclophosphamide dose

Additional risk factors associated with increased **FN across all cycles** of chemotherapy were<sup>3</sup>:

- low absolute neutrophil or white blood cell count
- cardiac comorbidity
- high planned doses of cytarabine or etoposide

Primary CSF prophylaxis was a protective factor against FN in the first cycle and across all cycles. These data have been submitted for publication.

Figure 1: Chemotherapy dose limitations for breast cancer and lymphoma patients



## STUDY GROUP MEETING



The latest INC-EU Study Group meeting took place on 8th September in Zurich, Switzerland.

## Other research activities of INC-EU Study Group members

Two recent reports describe the impact of reduced RDI on survival in lymphoma patients receiving CHOP-21 chemotherapy in the UK<sup>6</sup> and Belgium<sup>7</sup>. Both studies found that patient survival was reduced when RDI was  $\leq$  90%, indicating that patient outcome is improved when the intensity of chemotherapy treatment is optimal.

A recent audit by the South West London Cancer Network (communicated by Robert Leonard) recorded 71 hospital admissions for FN<sup>8</sup>. In 51 patients, this was the first episode of FN. The most frequent chemotherapy

regimens in these patients hospitalised for FN were CHOP, docetaxel, AC and FEC, and most episodes of FN occurred during the first two cycles. Mean time from arrival to start of antibiotic therapy was 2.6 hours and patients were hospitalised for a median of 5 days. Chemotherapy was delayed in 26% of patients and reduced in 19%. Four patients (5.6%) died during admission. Other studies have reported mortality rates of 9.5%<sup>9</sup> and 12%<sup>10</sup> in patients hospitalised for FN. FN still poses a significant risk of morbidity and mortality.

A retrospective sub-analysis of results from the GEPARTRIO study compared the efficacy

of four primary prophylaxis regimens against FN and related toxicities in 1,256 breast cancer patients who received TAC neoadjuvant chemotherapy<sup>11</sup>. Primary prophylaxis was intensified by stepwise protocol amendments resulting in four patient cohorts: ciprofloxacin, daily CSF, pegfilgrastim, pegfilgrastim and ciprofloxacin. Pegfilgrastim  $\pm$  ciprofloxacin was significantly more effective than either ciprofloxacin or six doses of daily CSF in preventing FN and reducing neutropenia-related hospitalisations. Daily CSF was significantly more effective than ciprofloxacin alone in reducing neutropenia-related hospitalisations.

## NEWS FROM AMERICA

The ANC study group is directed by American haematologists and oncologists Gary Lyman, David Dale and Jeffrey Crawford. The remainder of the study group comprises biostatisticians and other medical professionals from around the world.

### Abstracts presented at the 2008 ASCO meeting

- A prospective study of 1,202 breast cancer patients found that planned delivery of standard chemotherapy (RDI  $\geq$  85%) doubled the risk of FN and CIN over multiple cycles of treatment, whereas primary CSF prophylaxis was associated with reduced FN/CIN [#634].
- A prospective observational study reported predictors of RDI < 85% in 312 ovarian cancer patients to be obesity, low ECOG status and receipt of non-platinum chemotherapy regimens [#16508].
- In a prospective study of 4,458 consecutive adult cancer patients, treatment with pegfilgrastim (n = 1,209) was associated with increased progression-free survival and overall survival [#6552]. This effect was significant after adjustment for disease

stage, performance status, and various comorbidities.

- A prospective study of 521 colorectal cancer patients found that older patients experienced twice as many neutropenic complications as younger patients, and in general received a reduced RDI rather than CSF prophylaxis [#4052].

### Further publications by members of the ANC

- **'Cancer Supportive Care: Advances in Therapeutic Strategies'** is a new book that addresses not only classical cancer support issues such as pain and nausea control, but also approaches for managing the complete range of symptoms, toxicities and complications<sup>12</sup>.
- A prospective study of 976 **cancer patients aged  $\geq$  70** found that 50% of patients received an actual RDI < 85%. Increasing age was associated with lower RDI, and increasing age alone did not increase the risk of haematological toxicity<sup>13</sup>.
- An **economic analysis of pegfilgrastim** use found that once-per-cycle primary prophylactic treatment was cost-effective and cost-saving<sup>14</sup>.

## ANC COORDINATING CENTRE



The Coordinating Centre for the ANC Study Group has now relocated to Duke University, Durham, North Carolina.

- A study of **breast cancer patients** found that black women and women of lower socioeconomic status were more likely to receive non-standard adjuvant chemotherapy regimens<sup>15</sup>.
- Lyman et al. reviewed various **clinical practice guidelines** and found that all recommended the use of CSF where FN risk is  $\geq$  20%<sup>16</sup>.

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## IN THE LITERATURE...

Two recent meta-analyses examined the **impact of CSF use on the incidence of FN** and on incidence of early mortality. Data from 17 randomised controlled trials (RCTs) comparing CSF to placebo, including 3,493 patients with solid tumour or lymphoma, were evaluated<sup>17</sup>. **Primary CSF prophylaxis reduced the relative risk (RR) of FN by 46%, and reduced the RR of mortality by over 40%**. Average RDI was significantly higher in patients who received CSF compared with controls (95% vs. 87%). Musculoskeletal pain, an adverse event associated with all CSFs, was reported more frequently in CSF-treated patients. Five RCTs, involving 617 breast cancer and lymphoma patients, have compared daily CSF (filgrastim) with pegfilgrastim primary prophylaxis<sup>18</sup>. Pegfilgrastim showed greater clinical efficacy, reducing the risk of FN by 34% relative to filgrastim (median duration of administration, 11 days); incidence of neutropenia or bone pain was similar between the two forms of CSF.

Treatment outcome in patients with breast cancer is related to the dose intensity of chemotherapy. A retrospective analysis of 793 early stage breast cancer patients treated with adjuvant anthracycline-based non-taxane chemotherapy, found that disease-free survival and overall survival at 10 years follow-up were adversely affected by the number of delayed cycles, number of delayed days and RDI < 85%<sup>19</sup>. The authors concluded that the practice of delays/reductions in chemotherapy to restrict toxicity should be avoided to achieve maximal benefit.

Recent EORTC guidelines<sup>20</sup> for the use of CSF identified several treatment- and patient-related risk factors for FN. These are discussed in a recently published review, in the context of the management of breast cancer in Europe<sup>21</sup>. The review concludes that primary CSF support is recommended if the overall risk of FN is  $\geq 20\%$ , or if a reduction in dose-intensity is associated with a poorer outcome.

## UPDATE FROM EUROPEAN ONCOLOGY NURSING GROUP

The Training Initiative in Thrombocytopenia, Anaemia and Neutropenia (TITAN) course continues to be successful. Updated TITAN

2008 course materials have been launched and the first TITAN course in the Middle East recently took place.

Insight is a newsletter that represents the interests of the INC-EU Study Group. The newsletter is intended for a professional medical audience. The information contained in this newsletter is not intended as advice for patient treatment. The full prescribing information on any drugs must be consulted before use.

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## Forthcoming conferences

### 50th American Society of Hematology (ASH) meeting

6-9 December 2008, San Francisco, USA, [www.hematology.org](http://www.hematology.org)

### 31st Annual San Antonio Breast Cancer Symposium (SABCS)

December 10-14, 2008, San Antonio, Texas, USA, [www.sabcs.org](http://www.sabcs.org)

### NCCN Annual Congress: Clinical Practice Guidelines & Quality Cancer Care™

11-15 March 2009, Hollywood, Florida, USA, [www.nccn.org](http://www.nccn.org)

### 13th Congress of the European Hematology Association (EHA)

4 - 7 June 2009, Berlin, Germany, [www.ehaweb.org/congress/](http://www.ehaweb.org/congress/)

### European CanCER Organisation (ECCO) 15 and 34th European Society for Medical Oncology (ESMO) Congress

20 - 24 September 2009, Berlin, Germany, [www.esmo.org](http://www.esmo.org) or [www.ecco-org.eu](http://www.ecco-org.eu)

### 28th Annual European Society of Therapeutic Radiology and Oncology (ESTRO 28)

2009, TBC, [www.estro28.org](http://www.estro28.org)

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