1.1 Title:

Generic Chemotherapy Protocol Guidelines

1.2 Summary of the policy's objectives:
This guidance is intended to be used by all health-care professionals involved in the prescribing and delivery of systemic chemotherapy for cancer in the absence of protocol specific guidance or specific documented clinician-directed guidance.

1.3 What legislation or source documentation does this policy relate to?
See references at end of document

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SELCN Drugs and Therapeutics Advisory Committee

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Scope of Guidance

1) This guidance is intended to be used in the absence of protocol specific guidance or specific documented clinician-directed guidance.
2) Regimen specific protocols and guidelines should always be used where available. These are hosted on the South East London Cancer Network website at www.selcn.nhs.uk.
3) Alternatively if the treatment is part of a clinical trial the specific clinical trial protocol should be used as the reference source.
4) This guidance has been largely based on guidelines produced by the Essex Cancer Network with grateful thanks, for their kind permission.

Calculation of Body Surface Area (BSA)

Surface area is calculated using the Dubois & Dubois equation. This is the preferred calculation for this network, as it is used in the electronic prescribing systems already in use within the Network.

\[
SA = \frac{W^{0.425} \times H^{0.725} \times 71.84}{10,000}
\]

SA = body surface area in m\(^2\), W = weight in kg, H = height in cm

Surface area nomograms can be used, using the appropriate formula

Pre-programmed calculators are available but should be used with caution to ensure the correct formula is being used.

**Ideal vs actual weight**

BSA calculations should be based on actual weight unless the protocol specifies that actual or adjusted weight should be used e.g. some protocols for peripheral blood stem cell or bone marrow transplants

Calculation of Creatinine Clearance (CrCl)

At present there is no nationally agreed standard method for calculating creatinine clearance. Within SELCN, unless specified in individual protocols, the Cockcroft and Gault equation should be used to calculate creatinine clearance.

Creatinine Clearance (CrCl) is calculated using the Cockcroft & Gault equation:

\[
CrCl \text{ in mls/min} = \begin{cases} 
1.04 \times (140-\text{age in years}) \times (\text{wt in kg}) \\
\text{ Serum Creatinine in micromoles/L} \\
1.23 \times (140-\text{age in years}) \times (\text{wt in kg}) \\
\text{ Serum Creatinine in micromoles/L}
\end{cases}
\]

Other methods routinely used to measure renal function include. \(Cr^{51}\) EDTA clearance, eGFR (estimated GFR – based on the abbreviated MDRD equation) result which is available on EPR (Electronic Patient Record – at GSTT and Kings). In cancer we do not use the eGFR result to determine chemotherapy doses for patients with renal dysfunction.

Obese Patients

In line with the ASCO guidelines it has been agreed not to cap patients who have a surface area of 2m\(^2\) or more and that we should use actual body weight on the premise that:
We may be under-dosing many obese patients – especially when treatment is given with curative intent or in the adjuvant/neoadjuvant setting – and this may compromise outcome.

There is no data to support that these patients will have greater toxicity if doses are given based on actual weight compared with non-obese patients.

Fixed-dose chemotherapy is rarely justified (nb does not include drugs where there may be a max dose eg vincristine at 2mg or vinblastine at 10mg and a few select others).

Selection of dose at outset should be taken in the same context as for non-obese patients eg co-morbidities, PS, age/frailty.

Toxicity should be managed in the same way as for non-obese patients.

Calculation of the body mass index (BMI) can provide an individualised measure of obesity in those patients who are overweight due to excessive fatty tissue.

\[
\text{BMI} = \frac{\text{Weight (in kg)}}{\text{Height}^2 \text{ (in m)}}
\]

NB: Patients may be above a normal weight for their height but not obese e.g. body builders where additional muscular weight may be present.

The following BMI ranges are defined by the World Health Organisation:
- 25 to 29.9 Moderately Obese
- 30 to 39.9 Severely Obese
- > 40 Morbidly Obese

In general, doses of chemotherapy should NOT be capped for patients who are obese and doses should be modified on toxicity and tolerability. Clinician assessment should be considered on an individual basis. See below.

**Calculation of Chemotherapy Drug Doses**

- All chemotherapy doses should be prescribed according to dose banding within 5%. These tables may be provided on the individual prescription charts or on separate banding tables.
- Where individual doses have been prescribed and dose banding is relevant, the banded dose will be supplied by pharmacy and the chart endorsed accordingly, unless the prescription clearly states otherwise.
- For subsequent courses of chemotherapy, drug doses should be prescribed to the same dose as the previous cycle unless the recalculated target dose varies by more than 5% (ie change in weight) when compared to the last previously prescribed (administered) dose or toxicity indicates a dose change. In these cases doses should be re-prescribed as above.
- For oral chemotherapy, dose rounding may be needed to facilitate dispensing if tablets/capsules are available in particular strengths.

**Carboplatin and Renal Function**

**First Dose**

- The first dose of Carboplatin should be based on creatinine clearance, calculated using the Cockcroft & Gault equation. Previous creatinine values should be taken in to consideration when calculating the 1st dose.
- If the current serum creatinine value is below the lower limit of normal and/or is significantly lower (i.e. 20micromoles/l or more) than previous stable serial creatinine values over the last 3 months, the current creatinine value may not correlate well with GFR. In these circumstances it may be appropriate to base the calculation of creatinine clearance on a previous creatinine value which is more reflective of renal clearance, or undertake EDTA or a 24hr measured clearance.
NB:
1) In patients who are significantly overweight and/or have a low creatinine value, the Cockcroft & Gault equation may over estimate creatinine clearance.
2) Carboplatin is contraindicated in patients with severe myelosuppression, pre-existing severe renal impairment (with creatinine clearance of less than 20 ml per minute) and a history of severe allergic reaction to carboplatin or other platinum containing compounds.

Subsequent Doses
- These should only be recalculated if the serum creatinine changes by 20-30% or more compared to the serum creatinine used to calculate the previous dose.
- If the serum creatinine value falls significantly (i.e. 20 micromoles/l or more) consideration must be taken as to whether there is a real improvement in renal function (e.g. disease response leading to improved renal function) or reduced creatinine is due to non-renal factors (e.g. poor nutrition). For the latter, it may be appropriate to base the calculation of creatinine clearance on a previous creatinine value which is more reflective of renal clearance or undertake EDTA...
- An EDTA clearance should be requested if the calculated creatinine clearance (using C+G) is <60 ml/min or >120 ml/min.

Timing of Blood Samples and Other Relevant Tests

Baseline tests – prior to 1st cycle of treatment
FBC including differential, U&E’s, LFT’s, bone and any other appropriate tests should be taken within 2 weeks of the 1st cycle of treatment. Any treatment dependant tests outside of normal range or seen to be unstable should be repeated no earlier than 1 day before treatment.

Pre-treatment tests – prior to subsequent days/cycles of treatment
FBC including differential, U&E’s, LFT’s, bone and any other appropriate tests should be taken ideally the day before treatment but no earlier than shown in the following table:

<table>
<thead>
<tr>
<th>Interval since last treatment day</th>
<th>Blood tests to be taken no earlier than:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 days</td>
<td>1 day before treatment</td>
</tr>
<tr>
<td>14 days</td>
<td>2 days before treatment</td>
</tr>
<tr>
<td>21 or more days</td>
<td>3 days before treatment</td>
</tr>
</tbody>
</table>

Days = working days but preferably ‘actual days’
Blood results taken before the day of treatment which are below the thresholds described in section below should be repeated on the day of treatment to ensure pre-treatment tests are adequate.

Timing of Chemotherapy Treatment in Relation to Other Procedures

Blood transfusions:
Where possible blood transfusions should be given after chemotherapy has been completed. If clinical assessment of the patient indicates that a blood transfusion can not be delayed until chemotherapy is completed then the blood transfusion should be given and completed before chemotherapy is started.

Only in the case of medical emergencies should a blood transfusion be given during administration of a chemotherapy regimen.

Medical procedures e.g. drainage of ascitic fluid or pleural fluid:
These procedures should be completed before the chemotherapy regimen is started. Some chemotherapy agents partition in to fluid collections (acting as sanctuary sites) and may affect drug distribution and toxicity
Significant fluid collections may also affect calculation of body surface area and creatinine clearance calculations.

Only in the case of medical emergencies should such a procedure be undertaken during administration of a chemotherapy regimen.

Additional Points to Remember

- Some regimens may need premedication eg steroids 24 hours prior to docetaxel
- For additional information re vesicant and irritant iv drugs and management of extravasation please see intranet/network guidelines
- All patients have a prechemo/systemic therapy consultation with the specialist nurse on the Chemotherapy Day Unit following their consent to treatment. In particular the patient will be given an alert card with contact numbers in case of queries or in an emergency
- Patients receiving bisphosphonates must have a documented dental review prior to starting and must have up to date bloods. With subsequent cycles the blood result, namely renal function, from the previous 4 weeks can be used unless the patient is clinically less well

Dose Modifications due to Haematological Toxicity
Where Carboplatin is used, the AUC value may be reduced by a factor of 1 e.g. AUC6 to AUC5, AUC5 to AUC4 etc, when dose reductions are necessary.

Treatments given with curative intent:

The following applies to treatment days containing myelosuppressive drugs. Where the only drugs due are non-myelosuppressive, treatment should proceed unless excluded through other toxicity or clinical circumstances.

<table>
<thead>
<tr>
<th>Day 1 treatment</th>
<th>Delay, typically 1 week, if absolute neutrophil count (ANC) &lt; 1 x 10^9/L and/or platelet count &lt;100 x 10^9/L. (some protocols dictate &lt;75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-cycle treatment, such as day 8 or 15</td>
<td>Omit if ANC &lt; 1 x 10^9/L and/or platelet count &lt; 75 x 10^9/L.</td>
</tr>
<tr>
<td>Continuous daily chemotherapy, e.g. 5FU or Capecitabine</td>
<td>Inter-cycle doses are not omitted unless clinical circumstances require blood counts to be measured and toxicity indicates dose modification /omission. Patients who are neutropenic but otherwise well should normally continue their treatment - Clinician Review</td>
</tr>
</tbody>
</table>

1st delay:

- If delay < 1 week: continue treatment at current dosage.
- If delay > 1 week: discuss with clinician regarding appropriate action in the light of treatment plan e.g. consider appropriate supportive management such as maintaining current dosing schedule with granulocyte colony stimulating factors (GCSF) support or dose reductions.
- ≥ 2 delays: consider appropriate supportive management e.g. GCSF (see local policy).

Where growth factors are not indicated, reduce the dose of subsequent treatments by 20%
Dose Modifications due to Neutropenic Sepsis

- In cases where neutropenic sepsis has occurred requiring hospitalisation and/or intravenous antibiotics consider appropriate supportive management during chemotherapy e.g. GCSF (see local policy).

- Where growth factors are not indicated, reduce the dose of subsequent treatments by 20%.

Treatments given with palliative intent:

The following applies to treatment days containing myelosuppressive drugs. Where the only drugs due are non-myelosuppressive, treatment should proceed unless excluded through other toxicity or clinical circumstances.

| Day 1 treatment | Delay, typically 1 week, if absolute neutrophil count (ANC) < 1.0 x 10⁹/L and/or platelet count < 100 x 10⁹/L NB if patient has a poor performance status then N > than 1.5 may be appropriate |
| Inter-cycle treatment, such as day 8 or 15 | Omit if ANC < 1 x 10⁹/L and/or platelet count < 75 x 10⁹/L |
| Continuous daily chemotherapy, e.g. 5FU or Capecitabine | Inter-cycle doses are not omitted unless clinical circumstances require blood counts to be measured and toxicity indicates dose modification /omission. Patients who are neutropenic but otherwise well should normally continue their treatment - Clinician Review |

Duration and number of delays

1° delay: If delay < 1 week, continue treatment at current dosage
          If delay > 1 week, reduce the dose of subsequent treatments by 25%.

2° delay: Reduce the dose of subsequent treatments by 25%.

3° delay: Clinician review before further treatment.

Dose Modifications due to Neutropenic Sepsis

In cases where neutropenic sepsis has occurred requiring hospitalisation and/or intravenous antibiotics, reduce the dose of subsequent treatments by 25%.

Dose Modifications due to Non - Haematological Toxicity

Where Carboplatin is used, the AUC value may be reduced by a factor of 1 e.g. AUC6 to AUC5, AUC5 to AUC4 etc, when dose reductions are necessary.

Consult the current product literature (Summary of Product Characteristics) and grade according to the NCIC Common Toxicity Criteria.

Treatments given with curative intent:

< Grade 3 Apply appropriate supportive management and continue with current dosage.

Grade 3 or 4 Delay treatment until resolved to grade 0 or 1. Apply appropriate supportive management and continue with current dosage. If, despite appropriate supportive treatment, further delay is required consider reducing subsequent doses by 20% - clinician review.
Treatments given with palliative intent:

< Grade 3       Apply appropriate supportive management and continue with current dosage. If recurs
despite supportive management delay until resolved to grade 0 or 1. Reduce subsequent
doses by 25%

Grade 3 or 4    Delay treatment until resolved to grade 0 or 1. Reduce subsequent doses by 25%. If
recurs despite dose reduction omit further treatment until clinician review.

Dose Modifications due to impaired hepatic and/or renal function

Cisplatin and Renal Function

Creatinine Clearance based on Cockcroft & Gault equation.

1st dose effect  > 30% decrease in calculated creatinine clearance:-
If due to dehydration, correct deficit, recalculate clearance and dose accordingly
as below. If NOT due to dehydration withhold Cisplatin treatment until clinician
review. It may be inappropriate to continue with Cisplatin treatment.

Subsequent doses  Dose as below for both curative and palliative intent

<table>
<thead>
<tr>
<th>CrCL (ml/min)</th>
<th>Cisplatin dose</th>
</tr>
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<tbody>
<tr>
<td>&gt;60</td>
<td>100%</td>
</tr>
<tr>
<td>51-60</td>
<td>75%</td>
</tr>
<tr>
<td>40-50</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;40</td>
<td>consider carboplatin</td>
</tr>
</tbody>
</table>

NB: In patients who are significantly overweight and/or have a low creatinine value, the Cockcroft & Gault
equation may over estimate creatinine clearance.

Anthracyclines and Liver Function

Includes Doxorubicin & Epirubicin

<table>
<thead>
<tr>
<th>Bilirubin micromoles/L</th>
<th>Liver Enzymes</th>
<th>% Dose to be given</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>NAD</td>
<td>100%</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Elevated Enzymes</td>
<td>100%</td>
</tr>
<tr>
<td>20 to 40</td>
<td>+/- Elevated Enzymes</td>
<td>75%</td>
</tr>
<tr>
<td>41 to 60</td>
<td>+/- Elevated Enzymes</td>
<td>50%</td>
</tr>
<tr>
<td>61 to 90</td>
<td>+/- Elevated Enzymes</td>
<td>25%</td>
</tr>
<tr>
<td>90 +</td>
<td>+/- Elevated Enzymes</td>
<td>0%</td>
</tr>
</tbody>
</table>

References:
3. WHO
4. Individual Summary of Product Characteristics (SPC’s)
5. NCIC Common Toxicity Criteria (CTC) Grading