Is pharmacokinetically guided chemotherapy dosage a better way forward?

Chemotherapy is one of the corner stones of the present cancer therapy arsenal. Selection of drugs, combinations and schedules is frequently based on group statistics data, ideally from controlled studies. The antitumoral effects of the cytostatics have to be carefully balanced against their well-known side effects.

In the future, the selection of drugs and their combinations should be based on the individual analyses of relevant tumour biological factors and pharmacokinetic parameters aiming at a truly tailored therapy concept. Ideally, this should result in enhanced antitumoral effects without the expense of increased toxicity. This type of strategy is far removed from today’s high-dose chemotherapy concept. Marrow-supported high-dose chemotherapy is aiming at increasing antitumoral effects, but is almost invariably associated with markedly increased acute toxicity.

Dosage of chemotherapy is normally based on body surface area. Few data actually support the use of this method [1]. The main advantage is that the method is robust and widely accepted. The major disadvantage is that body surface area generally correlates poorly with liver function. This is a problem as quite a few currently used cytostatics are metabolised via the liver. In addition, the present dosage strategies will result in inter-patient variations in the area under curve (AUC)/clearance variations with several multiples [2–4]. Due to these obvious shortcomings, investigators have studied alternatives to body surface area-based dosage, one being pharmacokinetically guided therapy, the other toxicity-based therapy [5, 6]. The first approach is aimed at optimising drug dosage for inter-patient pharmacokinetic variability. In a randomised study on children with acute lymphoid leukaemia (ALL), the authors noticed a statistically significant improvement in outcome for the large subgroup with B-ALL when treated with pharmacokinetically guided therapy [5]. The latter principle was tested in a dose-escalated, tailored and G-CSF-supported FEC (5-fluorouracil, epirubicin, cyclophosphamide) regimen compared with standard FEC followed by the original CTCb (cyclophosphamide, thiopeta, carboplat) regimen for breast cancer treatment. The individually adapted FEC regimen resulted in fewer breast cancer relapses, less acute toxicity but also an increased risk for myelodysplasia and acute myeloid leukaemia (Table 1) [6]. A modified tailored dosage principle is currently being explored in another adjuvant study, SBG 2000-1, and a more dose intensive concept is presently planned for the adjuvant setting for the high-risk group.

In this issue of Annals of Oncology, a Dutch group explores the use of population based pharmacokinetics for a modified high-dose CTC regimen [7]. The CTC regimen used by the authors contains dose and scheduling modifications compared with the original CTCb regimen [7, 8].

The group analysed the pharmacokinetics for the used compound and the active compound 4-hydroxycyclophosphamide together with the main tiotepa metabolite tepa [7]. Accuracy, “within-day and between day precision” were tested and found to be very good [7]. Relationships between AUCs and toxicities were identified and the data were investigated with

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<tr>
<th>No. of patients</th>
<th>DFS/RFS (%)</th>
<th>OAS (%)</th>
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<tr>
<td></td>
<td>MSHD</td>
<td>Non-MST</td>
</tr>
<tr>
<td>81</td>
<td>68</td>
<td>63</td>
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<tr>
<td>78</td>
<td>48</td>
<td>62</td>
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<tr>
<td>525</td>
<td>63</td>
<td>72 (P = 0.04)</td>
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<tr>
<td>885</td>
<td>72 (P = 0.057)</td>
<td>65</td>
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<tr>
<td>783</td>
<td>61</td>
<td>60</td>
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<tr>
<td>398</td>
<td>62</td>
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*5-year follow-up results; other studies 3-year follow-up results.

DFS, disease-free survival; MSHD, marrow-supported high-dose therapy; Non-MST, non-marrowsupported therapy; OAS, overall survival; RFS, relapse-free survival.
logistic regression analyses. Veno-occlusive disease (VOD) is one serious and life-threatening complication of high-dose chemotherapy. Interestingly, the authors described a relationship between 4-hydrocyclophosphamide (the active metabolite of cyclophosphamide), AUC and VOD [7]. Only three of 45 patients developed VOD, accordingly the relationship was formally not statistically significant. Statistically significant relationships were demonstrated between: thiotepa and tepa AUCs and transaminase elevations; tepa AUC and mucosities; and carboplatin AUC and ototoxicity [7]. These are all very important findings. The optimal clinical application remains to be settled and the observed variations between courses must be considered in future studies.

Ideally, the inter-patient differences in pharmacokinetical profiles should be used for up-front individual chemotherapy dosage, aimed at maintaining antitumoural effects and reduced side effects. In the future, the individual pharmacokinetic profiles should be established before first drug administration, aided by pharmacogenomic profiling. In addition, this type of strategy should also allow a better drug selection up-front.

A more global comment in relation to the present paper is that marrow-supported adjuvant high-dose therapies have, so far, not resulted in survival improvements compared with anthracycline-based regimens with different dose intensity and total doses (Table 1). Accordingly, the marrow-supported high-dose concept should no longer be used outside controlled studies. The data, so far, support the development of therapy strategies, which better reflect the breast cancer biology. The use of pharmacokinetically guided therapy using population-based pharmacokinetics should be one important research avenue for further exploration.

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References