ONCODAILY MEDICAL JOURNAL

editorial

New Leukaemia Drugs

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There have been considerable progress in treating leukaemias since 1950 when the 1st effective anti-leukaemia drug was developed. In the Editorial I focus on anti-leukaemia drugs developed over the past 20 years. I divide my review into sections on acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia. Within each section I show progress since 1950, the pace of drug development and highlight 3 drug categories, chemotherapy, targeted therapy and immune therapy. There is insufficient space to discuss details of the > 50 drugs so I use Tables to indicate, where relevant, mechanisms of action. Next, I discuss several related issues. Lastly, I comment on what potential future developments. In this context I'm reminded of a quote variously attributed to quantum physicist Niels Bohr or baseball catcher Yogi Bera: It's difficult to make predictions, especially about the future. But we should also recall that the best way to predict the future is to invent it.

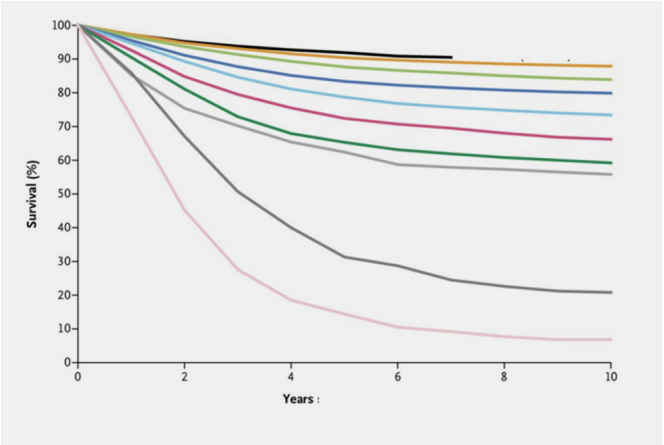

Figure 1. Progress in treating children with ALL

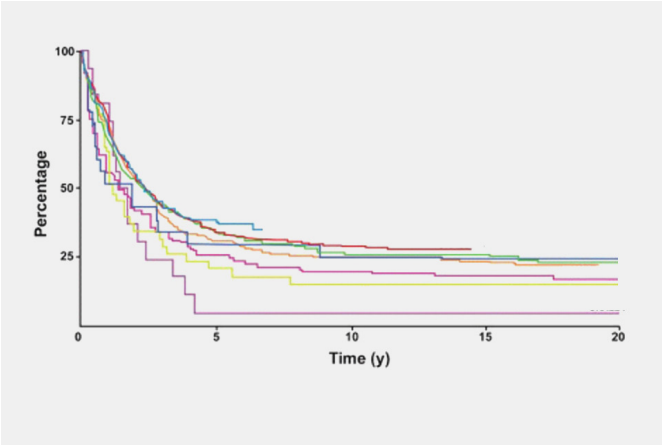

Figure 2. Progress in treating adults with ALL

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Table 1: New drugs for ALL	
Nelarabine	
Proteosome-inhibitors	Bortezomib, carfizomib, ixazomib
TKIs	Imatinib, dasatinib, nilotinib, ponatinib
BCL-2-inhibitors	Venetoclax
SKY-inhibitors	Entospletinib
TORC-1/-2	Sapanisertib
FGFR2	Pemigatinib
Antibodies	Blinatumomab, Inotuzumab
CAR-T-cells	Tisagenlecleucel, brexucabtagene autoleucel

Table 2: New drugs for AML	
	Liposomal cytarabine/daunorubicin
CC-486	Azacitidine
FLT3-inhibitors	Midostaurin, Gilteritinib, Quizartinib
IDH2	Enasidenib
IDH1	Ivosidenib, Olutasidenib
BCL-2	Venetoclax
Sonic Hedgehog	Glasdegib
FGFR2	Pemigatinib
Antibodies	Gemtuzumab
CAR-T-cells	None

Table 3. New drugs for CLL	
Bendamustine	
BTK-inhibitors	Ibrutinib, Acalabrutinib, Zanubrutinib, Pirtobrutinib, Orelabrutinib, Nemtabrutinib
BCL-2-inhibitor	Venetoclax
PI3K-inhibitor	Duvelisib, Idelalisib
Antibodies	Obinutuzumab, Rituximab hycela
CAR-T-cells	Lisocabtagene maraleucel

Acute lymphoblastic leukaemia

Figures 1 and 2 show progress in ALL therapy in children and adults over several decades. Progress in children had been remarkable, less so in adults. Drugs developed to treat ALL in the past 20 years are displayed in **Table 1.**

Acute myelogenous leukaemia

Figure 3 show progress in AML therapy over several decades. Figure 4 displays the timeline of drug development in AML indicating a rapidly accelerating pace of FDA-approvals. Drugs developed in the past 20 years to treat AML are displayed in Table 2; most are US FDA-approved.

Chronic lymphocytic leukaemia

Figure 5 show progress in CLL therapy over several decades focusing on people receiving therapy. Figure 6 displays a timeline of drug development in CLL indicating rapidly accelerating FDA-approvals. Drugs developed in the past 20 years to treat CLL are displayed in Table 3.

Chronic myelogenous leukaemia

Figure 7 shows the extraordinary progress in CML therapy since introduction of imatinib followed by several other tyrosine kinase-inhibitors. Figure 8 displays a timeline of drug development in CML. Drugs developed in the past 20 years to treat CML are displayed in Table 4 most of which are US FDA-approved. There is no approved immune therapy, perhaps because none is needed.

Comments

These data lead me to comments on several related issues including the long interval between basic research discoveries and 1st drug approval for a specific mechanism of action. Consider CML where it was > 60 years between discovery of the Ph-chromosome and approval of imatinib. This interval is substantially briefer for subsequent drugs with the same mechanism of action. For example, dasatinib, nilotinib, ponatinib, bosutinib and now asciminib relatively soon after approval of imatinib, gilteritinib and quizartinib after the approval of midostaurin, acalabrutinib and zanubrutinib after approval of ibrutinib and fe-

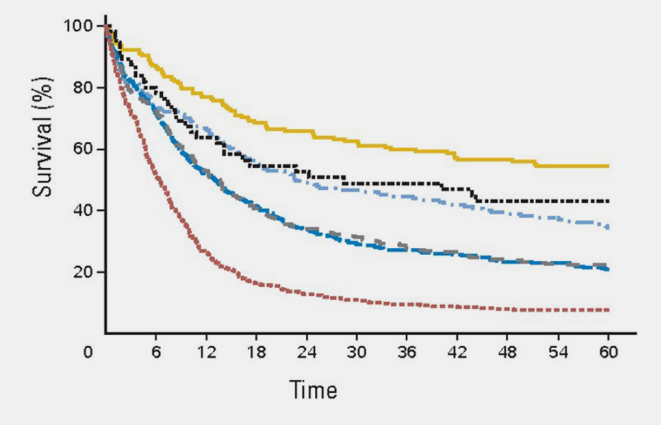

Figure 3. Progress in therapy of AML.

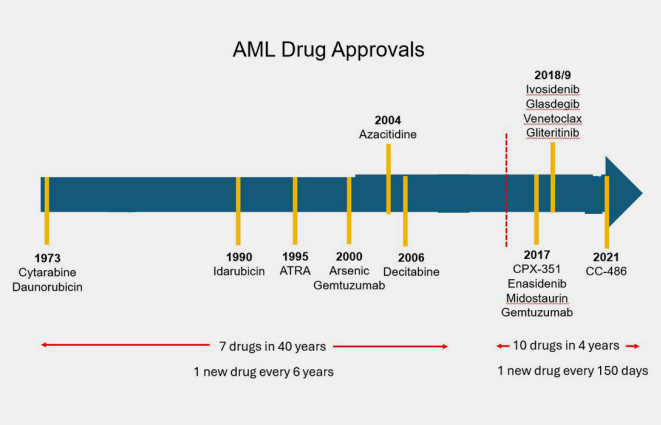

Figure 4. Timeline of drug development in AML

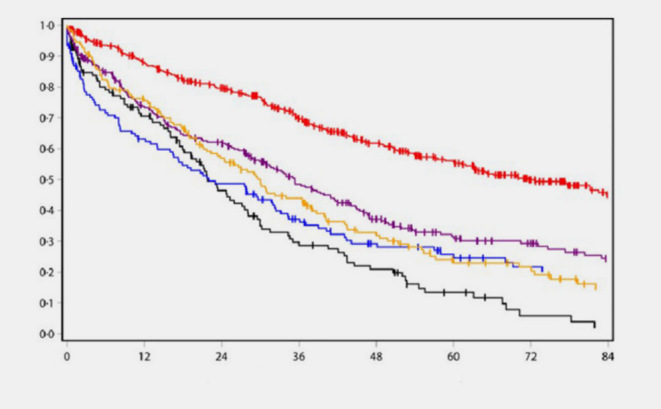

Figure 5. Progress in therapy of CLL (only people receiving therapy)

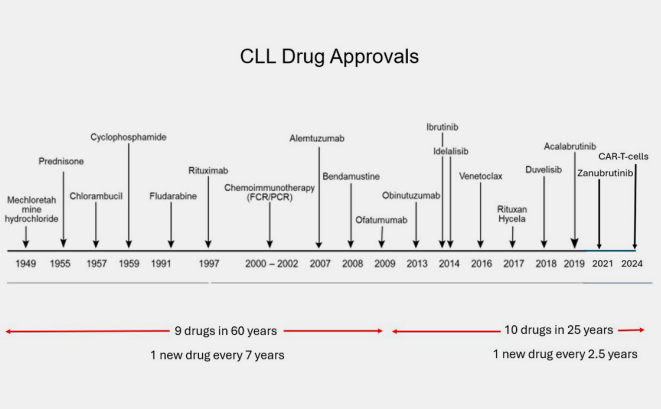

Figure 6. Timeline of drug development in CLL

dratinib, pancritinib and momelotinib relatively soon after approval of ruxolitinib.

Another striking related issue is the accelerating pace of drug approvals illustrated in Figures 4, 6 and 8. Some new derivative strategies include development of allosteric inhibitors (asciminib in CML) and non-covalent targeted therapies (pirtobrutinib in CLL). Another important development is the extraordinary rapid recent progress in immune therapies including monoclonal and bi-spcific antibodies and CAR-T-cells after a stagnant 50 years.

But our job is not done. Table 5 displays 5-year leukaemia survivals from the US SEER Registry. The CLL data includes people not receiving therapy, about one-half the population. Areas where we need to improve are in adults with ALL and AML and drugs for people failing current strategies. Use of haematopoietic cell transplants which I have not discussed is an example.

Lastly, the outcomes I reviewed are mostly from randomized controlled trials done in developed counties which are often unrepresentative of so-called real world results and results in developing countries for several reasons including selection biases, drug availability and economics. We need to get safe and effective drugs to people who need them. Figure 9 shows

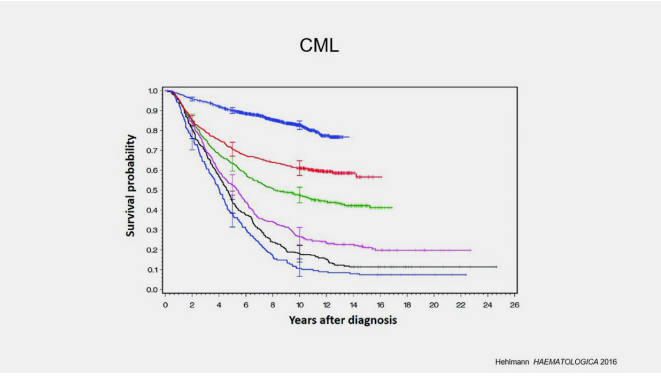

Figure 7. Progress in therapy of CML

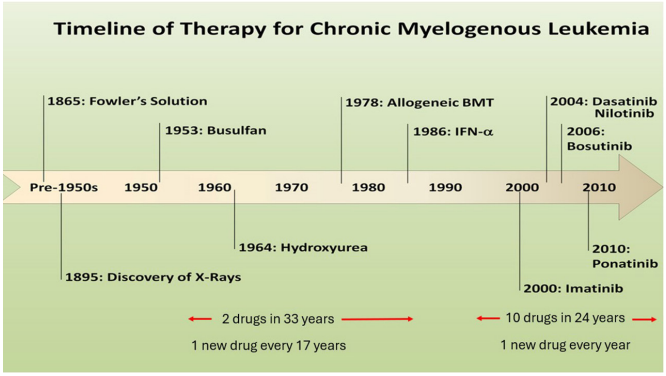

Figure 8. Timeline of drug development In CML

Table 4. New drugs for CML	
Omacetaxine	
TKIs	**Imatinib, Dasatinib, Nilotinib, Ponatinib, Bosutinib, Asciminib**
Antibodies	**None**
CAR-T-cells	**None**

Table 5. US Surveillance, Epidemiology End Results (SEER) 5-year survivals	
ALL	**72%**
AML	**30%**
CLL	**92%**
CML	**70-90%**

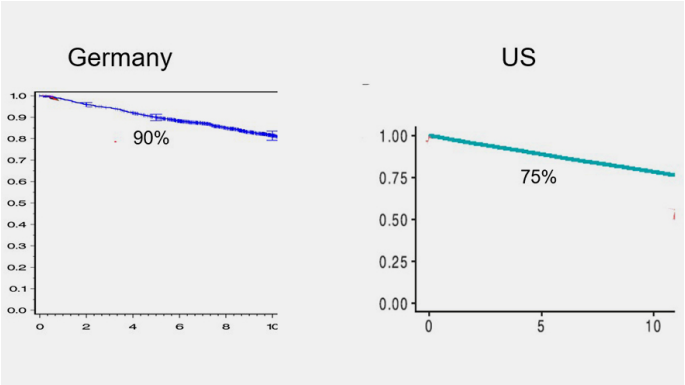

Figure 9. Comparison of survival in persons with CML between Germany and the US (Hehlmann R. LEUKEMIA 2017; Radivoyevitch T. LEUKEMIA 2020)

that even in the people in the US with CML drug access and compliance are sub-optimal.

Conclusions

There are many new safe and effective anti-leukaemia drugs accompanied by an accelerating pace of drug approvals. Much of this progress is driven by use of emerging technologies. However, we need to get new drugs to people who can benefit. Overall, there has been substantial progress but the job is not done.

Conflict of Interest

RPG is a consultant to Antengene Biotech LLC; Medical Director, FFF Enterprises Inc.; Speaker for Janssen Pharma and Hengrui Pharma; Board of Directors: Russian Foundation for Cancer Research Support; and Scientific Advisory Board: StemRad Ltd.

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Ethics Not applicable.